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(54) INHIBITORS OF HISTONE DEACETYLASE

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Description

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to the inhibition of histone deacetylase. More particularly, the invention relates to compounds, compositions and uses for inhibiting histone deacetylase enzymatic activity.

Summary of the Related Art

[0002] In eukaryotic cells, nuclear DNA associates with histones to form a compact complex called chromatin. The histones constitute a family of basic proteins which are generally highly conserved across eukaryotic species. The core histones, termed H2A, H2B, H3, and H4, associate to form a protein core. DNA winds around this protein core, with the basic amino adds of the histones interacting with the negatively charged phosphate groups of the DNA. Approximately 146 base pairs of DNA wrap around a histone core to make up a nucleosome particle, the repeating structural motif of chromatin.

[0003] Csordas, Biochem. J., 286: 23-38 (1990) teaches that histones are subject to posttranslational acetylation of the ε-amino groups of *N*-termina lysine residues, a reaction that is catalyzed by histone acetyl transferase (HAT1). Acetylation neutralizes the positive charge of the lysine side chain, and is thought to impact chromatin structure. Indeed, Taunton et al., Science, 272: 408-411 (1996), teaches that access of transcription factors to chromatin templates is enhanced by histone hyperacetylation. Taunton *et al*. further teaches that an enrichment in underacetylated histone H4 has been found in transcriptionally silent regions of the genome.

[0004] Histone acetylation is a reversible modification, with deacetylation being catalyzed by a family of enzymes termed histone deacetylases (HDACs). Grozinger et al., Proc. Natl. Acad. Sci. USA, 96: 4868-4873 (1999), teaches that HDACs may be divided into two classes, the first represented by yeast Rpd3-like proteins, and the second represented by yeast Hdal-lilce proteins. Grozinger *et al.* also teaches that the human HDAC1, HDAC2, and HDAC3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC4, HDAC5, and HDAC6, which are members of the second class of HDACs. Kao et al., Genes & Dev., 14: 55-66 (2000), discloses HDAC7, a new member of the second class of HDACs. Van den Wyngaert, FEBS, 478: 77-83 (2000) discloses HDAC8, a new member of the first class of HDACs.

[0005] Richon et al., Proc. Natl. Acad. Sci. USA, 95: 3003-3007 (1998), discloses that HDAC activity is inhibited by trichostatin A (TSA), a natural product isolated from *Streptomyces hygroscopicus,* and by a synthetic compound, suberoylanilide hydroxamic add (SAHA). Yoshida and Beppu, Exper. Cell Res., 177: 122-131 (1988), teaches that TSA causes arrest of rat fibroblasts at the G_1 and G_2 phases of the cell cycle, implicating HDAC in cell cycle regulation. Indeed, Finnin et al., Nature, 401: 1888-193 (1999), teaches that TSA and SAHA inhibit cell growth, induce terminal differentiation, and prevent the formation of tumors in mice.

[0006] These findings suggest that inhibition of HDAC activity represents a novel approach for intervening in cell cycle regulation and that HDAC inhibitors have great therapeutic potential in the treatment of cell proliferative diseases or conditions. To date, only a few inhibitors of histone deacetylase are known in the art. There is thus a need to identify additional HDAC inhibitors and to identify the structural features required for potent HDAC inhibitory activity.

BRIEF SUMMARY OF THE INVENTION

[0007] The invention provides compounds and methods for treating cell proliferative diseases. The invention provides new inhibitors of histone deacetylase enzymatic activity.

[0008] A document of Manfred Jung et al., entitled "Amide Analogues of Trichostatin A as Inhibitors of Histone Deacetylase and Inducers of Terminal Cell differentiation" (J. Med Chem. 1999, 42, 4669-4679) discloses amide analogues of trichostatin A as inhibitors of histone deacetylase with potential to induce terminal cell differentiation.

[0009] In a first aspect, therefore, the invention provides novel inhibitors of histone deacetylase. In one embodiment, the novel inhibitors of histone deacetylase are represented by formula (1):

$$Cy.\text{-}X\text{-}Y^1\text{-}W \qquad (1)$$

wherein

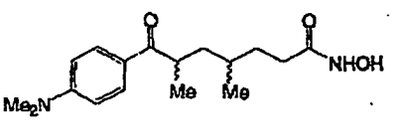
Cy is cycloalkyl, aryl, or a radical of a heterocyclic moiety, any of which may be optionally substituted;

X is selected from the group consisting of C=O, $C{=}CH_2$, CH(OH), $CH(QR^3)$, C=N(OH), and $C{=}N(OR^1)$, where R^1 is alkyl, aryl, aralkyl, or acyl; and where alkyl is a straight or branched chain saturated aliphatic group having from 1 to 12

carbon atoms, which may be substituted with one, two or three substituents;
Y^1 is a C_3-C_7 alkylene, wherein said alkylene may be optionally substituted, and wherein one or two carbon atoms in the linear chain connecting X and W may be replaced with O, NR^3, or $S(O)_n$, where R^3 is hydrogen, alkyl, aryl, aralkyl, sulfonyl, acyl, alkoxycarbonyl, or carbamoyl, and n is 0, 1, or 2, provided that the atoms in Y^1 that are attached to X and to W are carbon atom, and further provided that Y^1 does not comprise an ester or amide linkage, in the linear chain connecting X and W; and
W is selected from the group consisting of -C(O)-CH_2-SR^2,-C(O)-NH-OM, -NH-C(O)-NH-Z, and -C(O)-NH-Z, where R^2 is alkyl, aryl, aralkyl, or acyl, wherein the aryl portion of any such groups may be optionally substituted;
M is hydrogen or a pharmaceutically acceptable cation;
Z is selected from the group consisting of anilinyl, pyridyl, thiazolyl, hydroxyphenyl, thiadiazolyl, anilinylmethyl, or pyridylmethyl, any of which groups optionally may be substituted with halo, hydroxy, amino, nitro, C_1-C_4 alkyl, or C_1-C_4 alkoxy;
provided that X is C=CH_2, CH(OR^1), C=N(OH), or C=N(OR^1) when W is -C(O)-NH-OM and Cy is unsubstituted phenyl, dimethylaminophenyl, or methoxyphenyl; and
further provided that when W is -C(O)-CH_2-SR^2, the carbon atom in Y^1 that is attached to W is unsubstituted or is substituted with other than amino, acylamino, alkoxycarbonyl or carbamoyl; and further provided that when Cy is 2-methoxy-naphtyl, X is C=O and bounded to the position 6 of the said naphtyl, Y^1 is $(CH_2)_4$, W is different from C=O-NHOH, C=O-2-thiazolylamino, C=O-4-hydroxyanilino or C=O-2-hydroxyanilino.

[0010] A document of WV. Murray et al., entitled "Novel 6-oxo-6-naphtylhexanoic acid derivatives with anti-inflammatory and 5-lipoxygenase inhibitory activity" (Eur J Med Chem (1991) 26, 159-166) discloses that the compounds of formula (I) wherein Cy is 2-methoxy-naphtyl, X is C=O and bounded to the position 6 of the said naphtyl, Y^1 is $(CH_2)_4$, W is C=O-NHOR C=O-2-thiazolylamino, C=O-4-hydroxyanilino or C=O-2-hydroxyanilino have been found to be inhibitors of inflammation and 5-lipoxygenase.

[0011] In another embodiment, the novel inhibitor of histone deacetylase is represented by formula (5):



(5)

[0012] In a second aspect, the invention provides a pharmaceutical composition comprising an inhibitor of histone deacetylase represented by formula (1) or (5) and a pharmaceutically acceptable carrier, excipient, or diluent.

[0013] In a third aspect, the invention relates to the use of histone deacetylase for the manufacture of a medicament for the treatment of a celle proliferative disease, of a protozoal disease or of a fungal disease.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0014] The invention provides compounds for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and uses for treating cell proliferative diseases and conditions. The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art.

[0015] For purposes of the present invention, the following definitions will be used:

[0016] As used herein, the terms "histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from the ε-amino groups of lysine residues at the N-terminus of a histone. Unless otherwise indicated by context, the term "histone" is meant to refer to any histone protein, including H1, H2A, H2B, H3, H4, and H5, from any species. Preferred histone deacetylases include class I and class II enzymes. Preferably the histone deacetylase is a human HDAC, including, but not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8. In some other preferred embodiments, the histone deacetylase is derived from a protozoal or fungal source.

[0017] The term "Histone deacetylase inhibitor" or "inhibitor of histone deacetylase" is used to identify a compound having a structure as defined herein, which is capable of interacting with a histone deacetylase and inhibiting its enzymatic activity. Inhibiting histone deacetylase enzymatic activity means reducing the ability of a histone deacetylase to remove an acetyl group from a histone. In some preferred embodiments, such reduction of histone deacetylase activity is at least about 50%, more preferably at least about 75%, and still more preferably at least about 90%. In other preferred embodiments, histone deacetylase activity is reduced by at least 95% and more preferably by at least 99%.

[0018] Preferably, such inhibition is specific, *i.e.*, the histone deacetylase inhibitor reduces the ability of a histone deacetylase to remove an acetyl group from a histone at a concentration that is lower than the concentration of the

inhibitor that is required to produce another, unrelated biological effect. Preferably, the concentration of the inhibitor required for histone deacetylase inhibitory activity is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological effect.

[0019] The term "alkyl" as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms, preferably 1-8 carbon atoms, and more preferably 1-6 carbon atoms, which may be optionally substituted with one, two or three substituents. Unless otherwise explicitly stated, the term "alkyl" is meant to include saturated, unsaturated, and partially unsaturated aliphatic groups. When unsaturated groups are particularly intended, the terms "alkenyl" or "alkynyl" will be used. When only saturated groups are intended, the term "saturated alkyl" will be used. Preferred saturated alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, and hexyl.

[0020] An "alkylene" group is an alkyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. The term "alkylene" includes saturated, unsaturated and partially unsaturated alkyl groups. Where the term "alkylene" includes a descriptor indicating the number of carbon atoms or a range in the number of carbon atoms, *e.g.*, C_6 alkylene, the number of carbon atoms refers to the length of the linear chain connecting the two chemical groups between which the alkylene group is positioned. Any of the carbon atoms of the alkylene group may be optionally substituted, as described below, and the substituents may contain additional carbon atoms.

[0021] The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having from 3 to about 12 carbons, preferably from 3 to about 8 carbons, and more preferably from 3 to about 6 carbons, wherein the cycloalkyl group additionally may be optionally substituted. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0022] An "aryl" group is a C_6-C_{14} aromatic moiety comprising one to three aromatic rings, which may be optionally substituted. Preferably, the aryl group is a C_6-C_{10} aryl group. Preferred aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aralkyl," or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is (C_1-C_6)alk(C_6-C10)aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl. An "alkaryl" or "alkylaryl" group is an aryl group having one or more alkyl substituents. Examples of alkaryl groups include, without limitation, tolyl, xylyl, mesityl, ethylphenyl, tert-butylphenyl, and methylnaphthyl.

[0023] A "heterocyclic moiety" or "heterocyclyl" is a ring structure having from about 3 to about 8 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S. In some embodiments, the heterocyclic group is saturated or partially saturated. In these embodiments, the heterocyclic group may be optionally substituted on carbon at one or more positions, and may also independently be substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, aralkoxycarbonyl, or on sulfur with oxo or lower alkyl. Preferred saturated heterocyclic groups include, without limitation, epoxy, aziridinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, oxazolidinonyl, and morpholino. In certain preferred embodiments, the heterocyclic group is fused to an aryl or heteroaryl group. Examples of such fused heterocyles include, without limitation, tetrahydroquinoline and dihydrobenzofuran.

[0024] In some other embodiments, the heterocyclic moiety is a heteroaryl group. As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to about three heteroatoms selected from the group consisting of N, O, and S. Preferred heteroaryl groups include, without limitation, thienyl, benzothienyl, furanyl, benzofuranyl, dibenzofuranyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, quinoxalinyl, tetrazolyl, oxazolyl, thiazolyl, and isoxazolyl.

[0025] As employed herein, a "substituted" alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclic group is one having from one to about four, preferably from one to about three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo, oximino, nitro, haloalkyl, alkyl, alkaryl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, alkoxycarbonyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, acyl, acyloxy, cyano, and ureido groups.

[0026] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine.

[0027] As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent.

[0028] The term "acylamino" refers to an amide group attached at the nitrogen atom. The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom. The nitrogen atom of an acylamino or carbamoyl, substituent may be additionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom. Unless otherwise explicitly limited, the term "amino" is meant to include NH_2, alkylamino, dialkylamino, arylamino, aralkylamino, and cyclic amino groups.

[0029] The term "oximino" refers to a =N(OH) or =N(OR) group, wherein R is alkyl, aryl, aralkyl, sulfonyl, or acyl. Unless otherwise explicitly limited, the term "oximino" is meant to include oximes of either E- or Z-configuration, or

mixtures thereof.

[0030] The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

Compounds

[0031] In a first aspect, the invention provides novel inhibitors of histone deacetylase. In a first embodiment, the novel inhibitors of histone deacetylase are represented by formula (1):

$$Cy\text{-}X\text{-}Y^1\text{-}W \qquad (1)$$

wherein

Cy is cycloalkyl, aryl, or a radical of a heterocyclic moiety, any of which may be optionally substituted;

X is selected from the group consisting of C=O, $C=CH_2$, CH(OH), $CH(OR^1)$, C=N(OH), and $O=N(OR^1)$, where R^1 is alkyl, aryl, aralkyl, or acyl; and where alkyl is a straight or branched chain saturated aliphatic group having from 1 to 12 carbon atoms, which may be substituted with one, two or three substituents;

Y^1 is a C_3-C_7 alkylene, wherein said alkylene may be optionally substituted, and wherein one or two carbon atoms in the linear chain connecting X and W may be replaced with O, NR^3, or $S(O)_n$, where R^3 is hydrogen, alkyl, aryl, aralkyl, sulfonyl, acyl, alkoxycarbonyl, or carbamoyl, and n is 0,1, or 2, provided that the atoms in Y^1 that are attached to X and to W are carbon atoms, and further provided that Y^1 does not comprise an ester or amide linkage in the linear chain connecting X and W; and

W is selected from the group consisting of $-C(O)-CH_2-SR^2$, -C(O)-NH-OM, -NH-C(O)-NH-Z, and -C(O)-NH-Z, where R^2 is alkyl, aryl, aralkyl, or acyl, wherein the aryl portion of any such groups may be optionally substituted;

M is hydrogen or a pharmaceutically acceptable cation;

Z is selected from the group consisting of anilinyl, pyridyl, thiazolyl, hydroxyphenyl, thiadiazolyl, anilinylmethyl, or pyridylmethyl, any of which groups optionally may be substituted with halo, hydroxy, amino, nitro, C_1-C_4 alkyl, or C_1-C_4 alkoxy;

provided that X is $C=CH_2$, $CH(OR^1)$, C=N(OH), or $C=N(OR^1)$ when W is -C(O)-NH-OM and Cy is unsubstituted phenyl, dimethylaminophenyl, or methoxyphenyl; and

further provided that when W is $-C(O)-CH_2-SR^2$, the carbon atom in Y^1 that is attached to W is unsubstituted or is substituted with other than amino, acylamino, alkoxycarbonyl, or carbamoyl; and further provided that when Cy is 2-methoxy-naphtyl, X is C=O and bounded to the position 6 of the said naphtyl, Y^1 is $(CH_2)_4$, W is different from C=O-NHOH, C=O-2-thiazolylamino, C=O-4-hydroxyanilino or C=O-2-hydroxyanilino..

[0032] In certain preferred embodiments according to this aspect of the invention, Cy is C_3-C_{12} cycloalkyl, more preferably C_3-C_8 cycloalkyl, most preferably C_3-C_6 cycloalkyl, any of which may be optionally substituted. In certain other preferred embodiments, Cy is C_6-C_{14} aryl, more preferably C_6-C_{20} aryl, and most preferably phenyl or naphthyl, any of which may be optionally substituted.

[0033] In still yet other preferred embodiments, Cy is a radical of a heterocyclic moiety. In some preferred embodiments, the heterocycle is selected from the group consisting of thiophene, benzothiophene, furan, benzofuran, pyridine, quinoline, indole, isoquinoline, thiazole, morpholine, piperidine, and piperazine, any of which may be optionally substituted.

[0034] Unless otherwise stated, substituted alkyl, aryl, or heterocyclic groups preferably have from one to about four, preferably from one to about three, more preferably one or two substituents, which are preferably selected from the group consisting of C_1-C_4 alkyl, preferably C_1-C_4 alkyl; halo, preferably Cl, Br, or F; haloalkyl, preferably $(halo)_{1\text{-}5}(C_1\text{-}C_6)$ alkyl, more preferably $(halo)_{1\text{-}5}(C_1\text{-}C_3)$alkyl, and most preferably CF_3; C_1-C_6 alkoxy, preferably methoxy, ethoxy, or benzyloxy; C_6-C_{10} aryloxy, preferably phenoxy; heteroaryloxy; C_1-C_6 alkoxycarbonyl, preferably C_1-C_3 alkoxycarbonyl, most preferably carbomethoxy or carboethoxy; C_6-C_{10} aryloxycarbonyl, preferably carbophenoxy; heteroaryloxycarbonyl; C_6-C_{10} aryl, preferably phenyl; $(C_6\text{-}C_{10})ar(C_1\text{-}C_6)$alkyl, preferably $(C_6\text{-}C_{10})ar(C_1\text{-}C_3)$alkyl, more preferably benzyl, naphthylmethyl or phenethyl; hydroxy$(C_1\text{-}C_6)$alkyl, preferably hydroxy$(C_1\text{-}C_3)$alkyl, more preferably hydroxymethyl; amino$(C_1\text{-}C_6)$alkyl, preferably amino$(C_1\text{-}C_3)$alkyl, more preferably aminomethyl; $(C_1\text{-}C_6)$alkylamino, preferably methylamino, ethylamino, or propylamino; di-$(C_1\text{-}C_6)$alkylamino, preferably dimethylamino or diethylamino; $(C_1\text{-}C_6)$alkylcarbamoyl, preferably methylcarbamoyl, dimethylcarbamoyl, or benzylcarbamoyl; $(C_6\text{-}C_{10})$arylcarbamoyl, preferably phenylcarbamoyl; $(C_1\text{-}C_6)$alkaneacylamino, preferably acetylamino; $(C_6\text{-}C_{10})$areneacylamino, preferably benzoylamino; $(C_1\text{-}C_6)$alkanesulfonyl, preferably methanesulfonyl; $(C_1\text{-}C_6)$alkanesulfonamido, preferably methanesulfonamido; $(C_6\text{-}C_{10})$arenesulfonyl, preferably benzenesulfonyl or toluenesulfonyl; $(C_6\text{-}C_{10})$arenesulfonamido, preferably benzenesulfonyl or toluenesulfonyl; $(C_6\text{-}C_{10})ar(C_1\text{-}C_6)$alkylsulfonamido, preferably benzylsulfonamido; C_1-C_6 alkylcarbonyl, preferably C_1-C_3 alkylcarbonyl, more preferably acetyl; $(C_1\text{-}C_6)$acyloxy, preferably acetoxy; cyano; amino; carboxy; hydroxy; ureido; and nitro. One or more carbon atoms of an alkyl, cycloalkyl, or heterocyclyl group may also be optionally substituted with an oxo or oximino group.

[0035] In some preferred embodiments, Cy is substituted by one or two substituents independently selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_6-C_{10} aryl, $(C_6\text{-}C_{10})ar(C_1\text{-}C_6)$alkyl, halo, nitro, hydroxy, C_1-C_6 alkoxy,

C_6-C_{10} aryloxy, heteroaryloxy, C_1-C_6 alkoxycarbonyl, C_6-C_{10} aryloxycarbonyl, heteroaryloxycarbonyl, carboxy, and amino. Preferably, the amino group is selected from the group consisting of NH_2, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_6-C_{10})arylamino, and (C_6-C_{10})ar(C_1-C_6)alkylamino.

[0036] In certain particularly preferred embodiments, Cy has the formula -Cy^1-Cy^2 or -Cy^1-G-Cy^2, wherein Cy^1 and Cy^2 are independently C_3-C_6 cycloalkyl, C_6-C_{10} aryl, or a radical of a heterocyclic moiety, which groups optionally may be substituted, and G is O, NR^3, or $S(O)_n$, where R^3 is hydrogen, alkyl, aryl, aralkyl, sulfonyl, acyl, alkoxycarbonyl, or carbamoyl, and n is 0, 1, or 2. Preferably, Cy^1 and Cy^2 are independently selected from the group consisting of phenyl, pyridinyl, morpholinyl, piperidinyl, piperazinyl, which groups optionally may be substituted.

[0037] In some preferred embodiments, X is C=O, $C=CH_2$, C=N(OH), and $C=N(OR^1)$, where R^1 is C_1-C_6 alkyl, C_6-C_{20} aryl, or (C_6-C_{10})ar(C_1-C_6)alkyl. More preferably, R^1 is C_1-C_4 alkyl, and still more preferably R^1 is methyl. When X is C=N(OH) or $C=N(OR^1)$, it may be in either the (E)- or (Z)-configuration, or it may be a mixture of the two. In some preferred embodiments, the C=N(OH) or $C=N(OR^1)$ group is in the (E)-configuration. Most preferably, X is C=O or C=N(OH), provided, however, that X is not C=O when W is -C(O)-NH-OM and Cy is unsubstituted phenyl, dimethylaminophenyl, or methoxyphenyl.

[0038] In some other preferred embodiments, X is CH(OH) or $CH(OR^1)$, where R^1 is C_1-C_6 alkyl, C_6-C_{10} aryl, or (C_6-C_{10})ar(C_1-C_6)alkyl. The CH(OH) or $CH(OR^1)$ group may be of either (R)- or (S)-stereochemistry, or it may be a mixture of the two. Preferably, X is CH(OH) or $CH(OR^1)$, where R^1 is C_1-C_4 alkyl, provided, however, that X is not CH(OH) when W is -C(O)-NH-OM and Cy is unsubstituted phenyl, dimethylaminophenyl, or methoxyphenyl. In certain particularly preferred embodiments, X is CH(OMe).

[0039] Y^1 is a C_3-C_7 alkylene, wherein said alkylene may be optionally substituted. Preferably Y^1 is a C_4-C_7 alkylene, more preferably a C_5-C_7 alkylene, and most preferably a C_5 or C_6 alkylene. The alkylene may be saturated, unsaturated, or partially unsaturated. In certain preferred embodiments, Y^1 comprises an all-carbon linear chain connecting X and W. In certain other preferred embodiments, one or two carbon atoms in the linear chain connecting X and W are replaced with O, NR^3, or $S(O)_n$, where R^3 is hydrogen, alkyl, aryl, aralkyl, sulfonyl, acyl, alkoxycarbonyl, or carbamoyl, and n is 0,1, or 2, provided that the atoms in Y^1 that are attached to X and to W are carbon atoms, and further provided that Y^1 does not comprise an ester or amide linkage in the linear chain connecting X and W. In certain particularly preferred embodiment, Y^1 is -(CH_2)-$S(O)_n$-$(CH_2)_p$, where n is 0, 1, or 2, and p is 3,4, or 5.

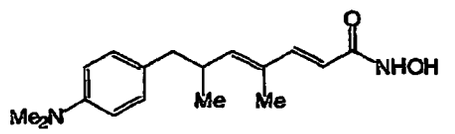
In some preferred embodiments, Y^1 is fully saturated and has the formula -$(CH_2)_m$, where m is 5, 6, or 7.

[0040] In some preferred embodiments, W is -C(O)-NH-OM, M being hydrogen or any pharmaceutically acceptable cation. Examples of pharmaceutically acceptable cations include, without limitation, sodium, potassium, magnesium, and calcium.

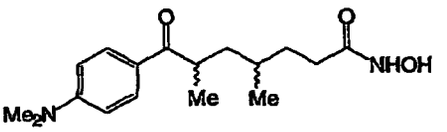
[0041] In some other preferred embodiments, W is -C(O)-CH_2-SR^2. R^2 is preferably selected from the group consisting of alkyl, preferably C_1-C_6 alkyl, more preferably C_1-C_4 alkyl, most preferably methyl; aryl, preferably C_6-C_{10} aryl, more preferably phenyl or naphthyl; aralkyl, preferably (C_6-C_{10})ar(C_1-C_6)alkyl, more preferably (C_6-C_{10})ar(C_1-C_4)alkyl, most preferably benzyl or naphthylmethyl; alkylcarbonyl, preferably (C_1-C_6 alkyl)carbonyl, more preferably (C_1-C_4 alkyl)carbonyl, still more preferably acetyl; arylcarbonyl, more preferably (C_6-C_{10} aryl)carbonyl, still more preferably benzoyl; and aralkylcarbonyl, preferably (C_6-C_{10})ar(C_1-C_6)alkylcarbonyl, more preferably (C_6-C_{10})ar(C_1-C_4)alkylcarbonyl, still more preferably benzylcarbonyl The aryl portion of any such groups may be optionally substituted.

[0042] In some other preferred embodiments, W is -C(O)-NH-Z or NH-C(O)-NH-Z. Z is preferably selected from the group consisting of anilinyl, pyridyl, thiazolyl, hydroxyphenyl, thiadiazolyl, anilinylmethyl, or pyridylmethyl, any of which groups optionally may be substituted with halo, hydroxy, amino, nitro, C_1-C_4 alkyl, or C_1-C_4 alkoxy. More preferably, Z is selected from the group consisting of 2-anilinyl, 2-pyridyl, 2-hydroxyphenyl, 1,3,4-thiadiazol-2-yl, 2-anilinylmethyl, and 2-pyridylmethyl. In certain particularly preferred embodiments, Z is unsubstituted 2-anilinyl or unsubstituted 2-pyridyl. hydroxy(C_1-C_6)alkyl, more preferably hydroxy(C_1-C_3)alkyl, and still more preferably hydroxyethyl; acyl, preferably C_1-C_6 alkylcarbonyl, or C_6-C_{10} arylcarbonyl, more preferably C_1-C_3 alkylcarbonyl or C_6-C_{10} arylcarbonyl, more preferably acetyl or benzoyl; acyloxy, preferably C_1-C_6 alkylcarbonyloxy or C_6-C_{10} arylcarbonyloxy, more preferably C_1-C_3 alkylcarbonyloxy or C_6-C_{10} arylcarbonyloxy, and still more preferably acetoxy or benzoyloxy; and cyano.

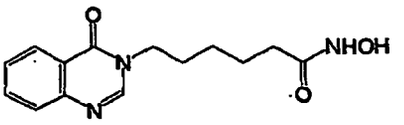
[0043] In a still yet another embodiment, the novel histone deacetylase inhibitor is represented by one of formulae (4)-(7):



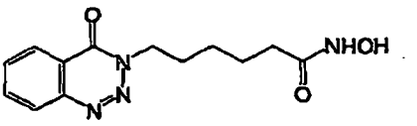
(4)



(5)



(6)

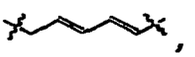


(7)

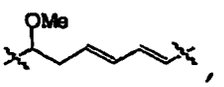
Synthesis

[0044] The following synthesis example is for illustration purpose only.

[0045] Compounds of formula (1), wherein Y^1 has the structure



or formula (2), wherein Y^2 has the structure



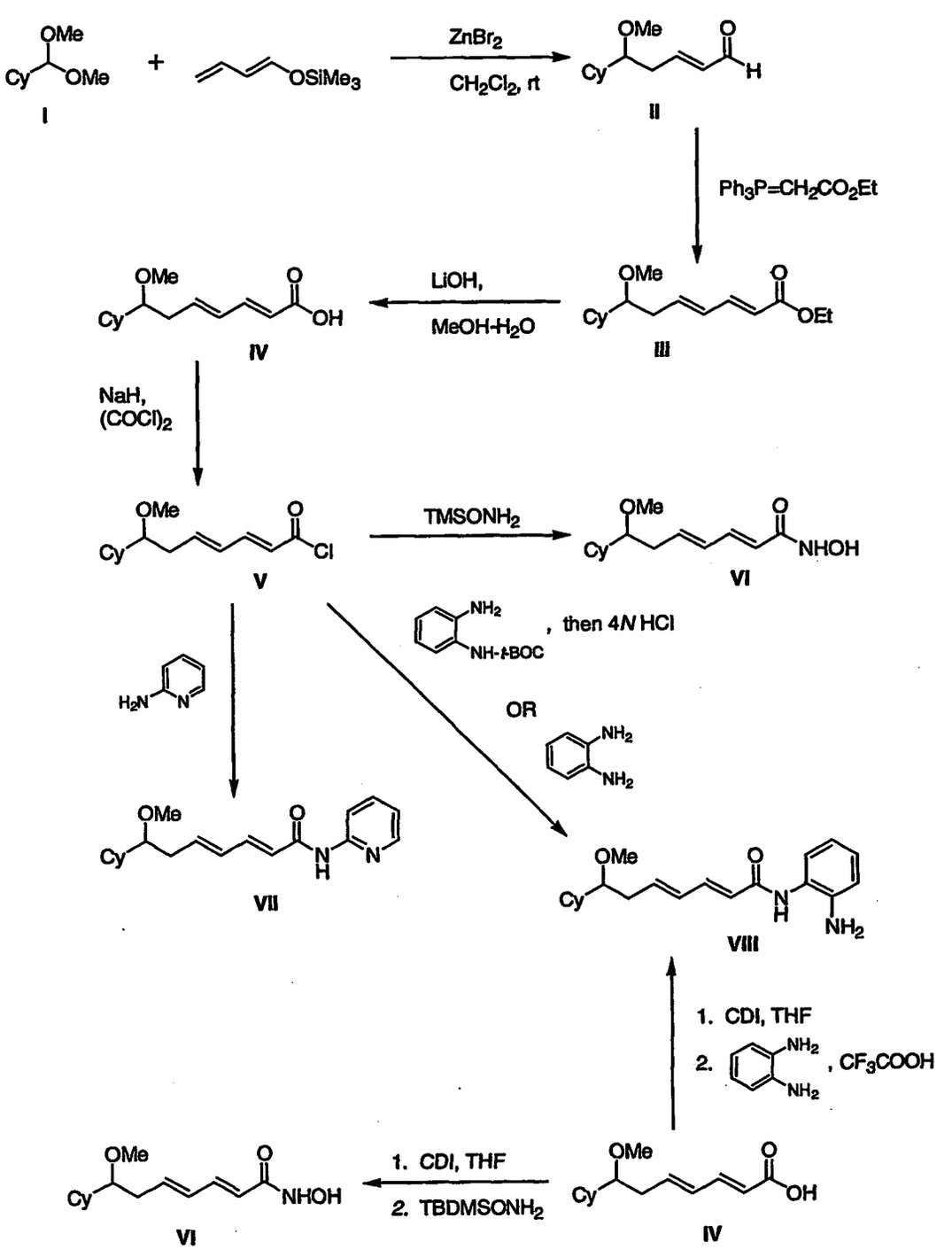
preferably may be prepared according to the synthetic route depicted in Scheme 1. Thus, a dialkyl acetal I is treated with 1-trimethylsilyloxy-1,3-butadiene in the presence of zinc bromide to afford the aldehyde **II.** Wittig reaction of **II** with a carboalkoxy phosphorous ylid such as ethyl (triphenylphosphoranylidene)acetate affords the diene ester **III.** Hydrolysis of the ester function in **III** can be effected by treatment with a hydroxide base, such as lithium hydroxide, to afford the corresponding acid **IV.**

[0046] The acid **IV** is converted to the corresponding acid chloride **V** according to standard methods, e.g., by treatment with sodium hydride and oxalyl chloride. Treatment of **V** with 2-aminopyridine and a tertiary base such as *N*-methylmorpholine, preferably in dichloromethane at reduced temperature, then affords the pyridyl amide **VII.** In a similar fashion, the acid chloride **IV** may be treated with 1,2-phenylenediamine to afford the anilinyl amide **VIII.** Alternatively, the acid chloride **V** may be treated with a mono-protected 1,2-phenylenediamine, such as 2-(t-BOC-amino)aniline, followed by deprotection, to afford **VIII.**

[0047] In another alternative procedure, the acid **IV** may be activated by treatment with carbonyldiimidazole (CDI), followed by treatment with 1,2-phenylenediamine and trifluoroacetic acid to afford the anilinyl amide **VIII.**

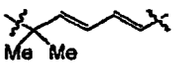
[0048] Similar procedures may be employed for the preparation of the hydroxamic acid **VI.** Thus, in some embodiments, the acid **IV** is converted to the corresponding acid chloride **V,** followed by the addition of a protected hydroxylamine such as *O*-trimethylsilylhydroxylamine in a solvent such as methylene chloride to form an *O*-silyl hydroxamate, which then provides the hydroxamic acid **VI** upon workup.

Scheme 1

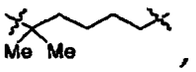


[0049] Alternatively, in some other embodiments, the acid **IV** is directly coupled with a protected hydroxylamine, such as *tert*-butyldimethylsilylhydroxylamine ($TBDMSONH_2$). The coupling reaction is preferably accomplished with a coupling reagent such as carbonyldiimidazole (CDI) in a solvent such as tetrahydrofuran (THF). Other coupling reagents are known in the art and may also be used for this reaction. When the protected hydroxylamine is a silylhydroxylamine, hydrolysis of the silyl ester occurs upon workup to afford the hydroxamic acid **VI**. When other protected hydroxylamines are employed, a separate deprotection step may be required.

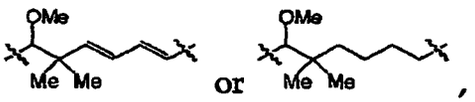
[0050] Compounds of formula (1), wherein Y^1 has the structure



(For illustration purpose only) or



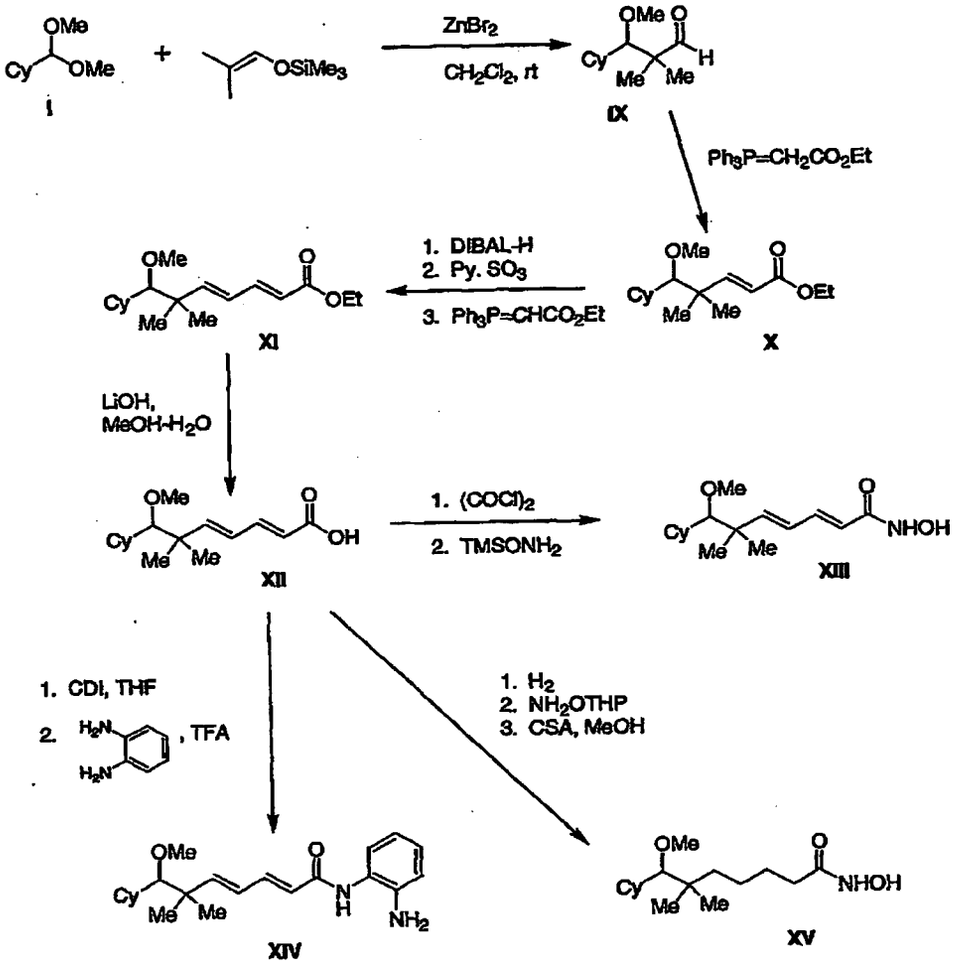
and compounds of formula (2), wherein Y^2 has the structure



(For illustration purpose only) preferably may be prepared according to the synthetic route depicted in Scheme 2. Thus, a dialkyl acetal **I** is treated with 2 methyl-1-(trimethylsilyloxy)-1-propene in the presence of zinc bromide to afford the aldehyde **IX.** Wittig reaction of **IX** with a carboalkoxy phosphorous ylid such as ethyl (triphenylphosphoranylidene) acetate affords the α,β-unsaturated ester **X.** The ester function in **X** is reduced to the alcohol with a reducing agent such as DIBAL-H, and then reoxidized to the corresponding aldehyde with an oxidizing agent such as pyridinium sulfur trioxide complex. Other reducing and oxidizing agents are well known in the art, and may also be used in these reactions.

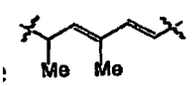
[0051] Homologation of the resultant aldehyde is accomplished by treatment with a carboalkoxy phosphorous ylid such as ethyl (triphenylphosphoranylidene)-acetate to afford the diene ester **XI,** which is hydrolyzed by treatment with a hydroxide base, such as lithium hydroxide to provide the corresponding acid **XII.** The remaining synthetic steps proceed as described above for Scheme 1.

Scheme 2

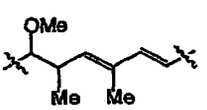


[0052] The following synthesis example is for illustration purpose only.

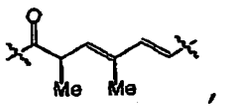
[0053] Compounds of formula (1), wherein Y^1 has the structure



and compounds of formula (2), wherein Y^2 has the structure

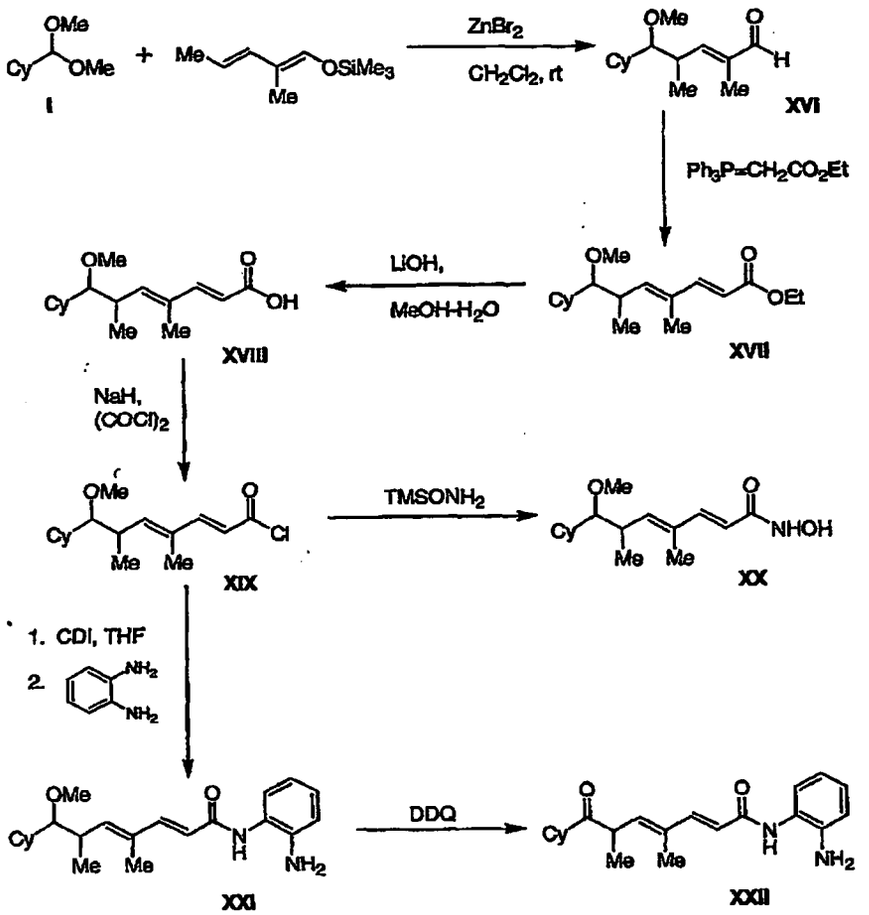


preferably may be prepared by procedures analogous to those already described, as illustrated in Scheme 3. Compounds **XXII**, wherein Y^2 has the structure



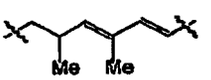
may be prepared from the corresponding methoxy substituted compounds **XXI** by oxidation with 2,3dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

Scheme 3



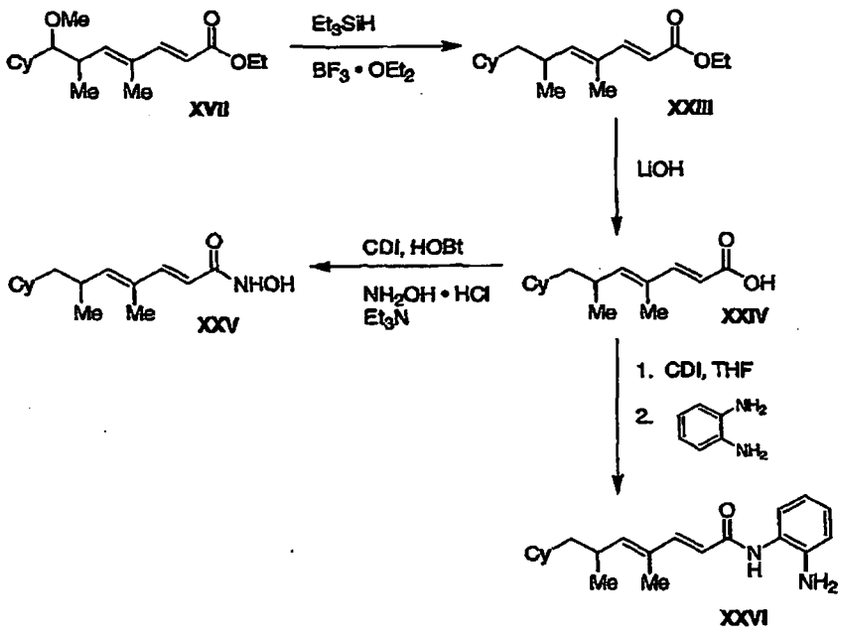
[0054] The following synthesis example is for illustration purpose only.

[0055] Compounds of formula (2), wherein Y^2 has the structure



preferably may be prepared as outlined in Scheme 4. Thus, the methoxy substituted diene ester **XVII,** prepared as described in Scheme 3, is treated with triethylsilane and boron trifluoride etherate to afford the deoxygenated compound **XXIII.** Conversion of **XXIII** to the hydroxamic acid **XXV** and the anilinylamide **XXVI** is accomplished by procedures analogous to those described above for Schemes 1-3.

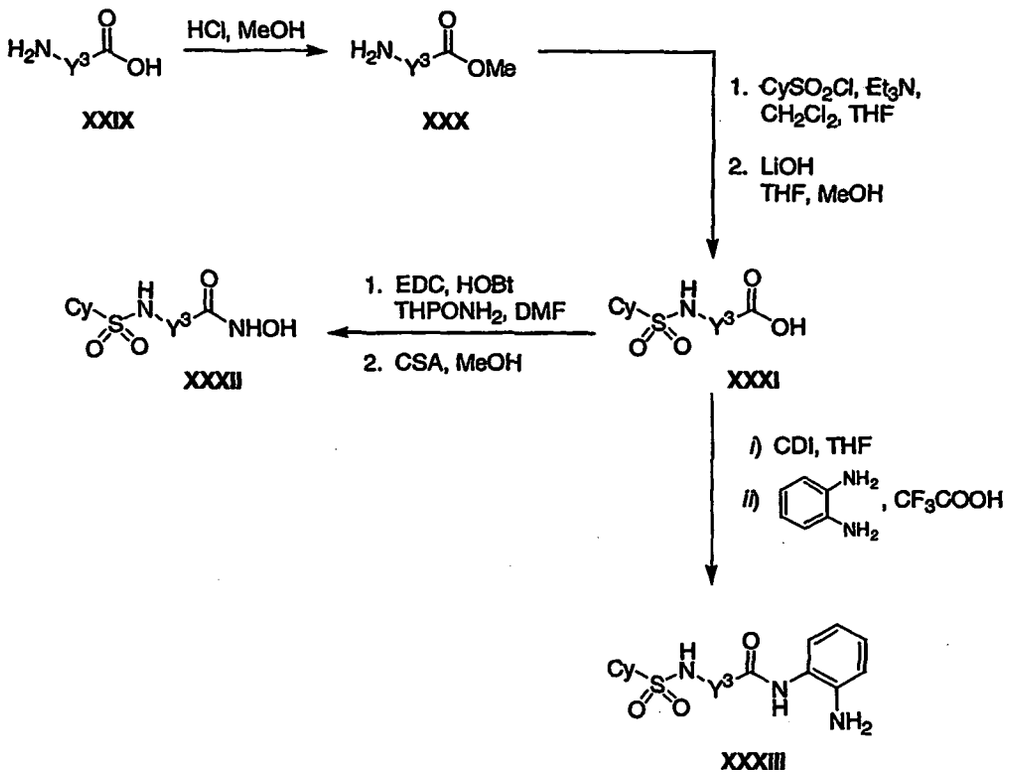
Scheme 4



[0056] The following synthesis example is for illustration purpose only.

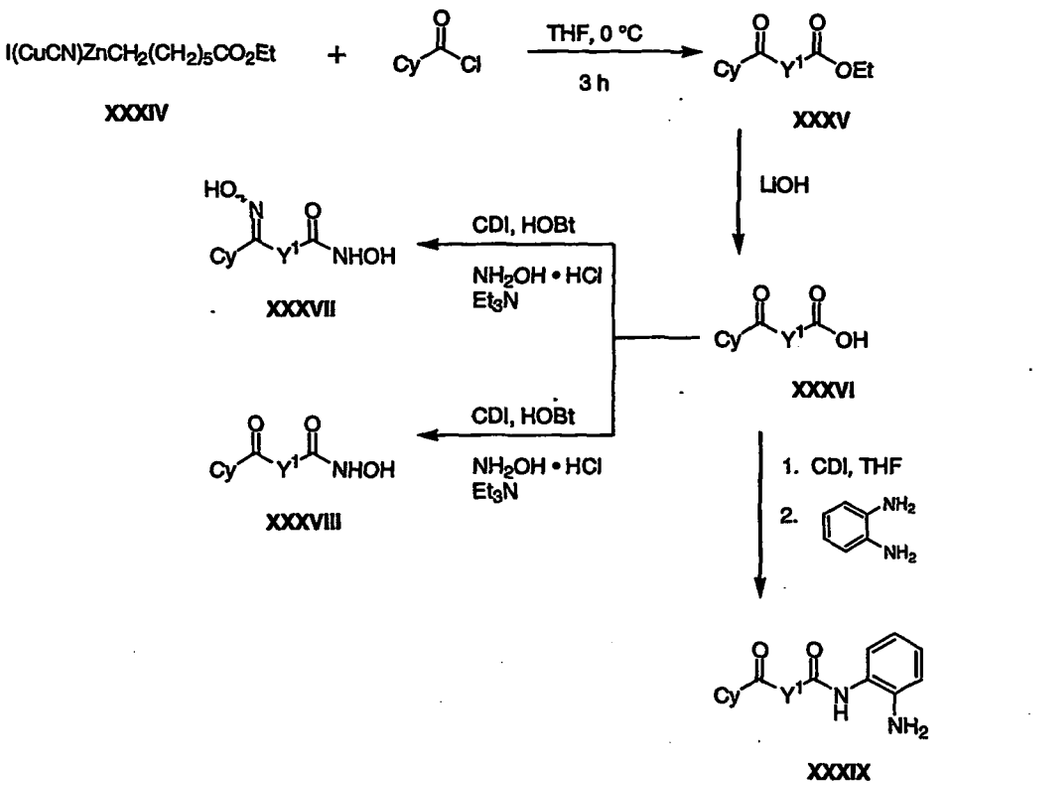
[0057] The compounds of formula (3) are preferably prepared as outlined in Scheme 5. Thus, an acid of formula **XXIX** is esterified and then treated with a sulfonyl chloride, preferably in the presence of a tertiary amine such as triethylamine. Saponification with a base such as LiOH then affords the acid **XXXI.** Conversion of **XXXI** to the hydroxamic acid **XXXII** and the anilinylamide **XXXIII** is accomplished by procedures analogous to those described above for Schemes 1-3.

Scheme 5



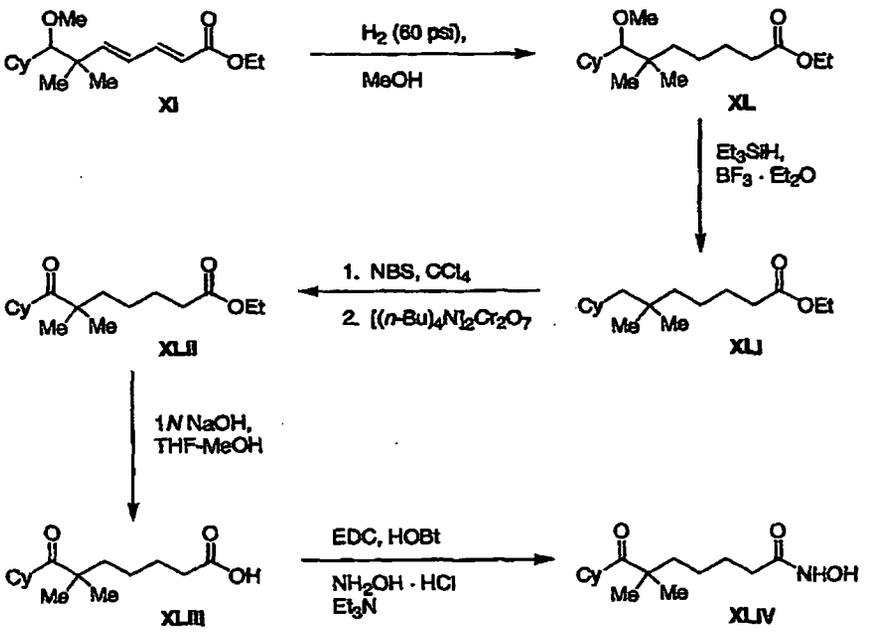
[0058] Compounds of formula (1), wherein X is C=O or C=N(OH) are preferably prepared as outlined in Schemes 6 and 7. Thus, an acyl chloride is treated with the heterocuprate reagent **XXXIV** in a solvent such as THF to afford the ketone **XXXV.** Ester hydrolysis affords the acid **XXXVI,** which may be coupled with hydroxylamine or with 1,2-phenylenediamine to afford the hydroxamic acid **XXXVIII** or the anilinylamide **XXXIX,** respectively. Alternatively, coupling of the acid **XXXVI** with an excess of hydroxylamine affords the oximino hydroxamic acid **XXXVII.**

Scheme 6



[0059] Hydrogenation of the dienyl ester **XI** affords the saturated derivative **XL,** which is deoxygenated by treatment with triethylsilane and borontrifluoride etherate. Benzylic oxidation is then accomplished by treatment with N-bromosuccinimide in carbon tetrachloride, followed by treatment with bis(tetrabutylammonium) dichromate to afford the ketone **XLII.** Ester hydrolysis and conversion to the hydroxamic acid are then accomplished by procedures analogous to those described above for Schemes 1-3.

Scheme 7

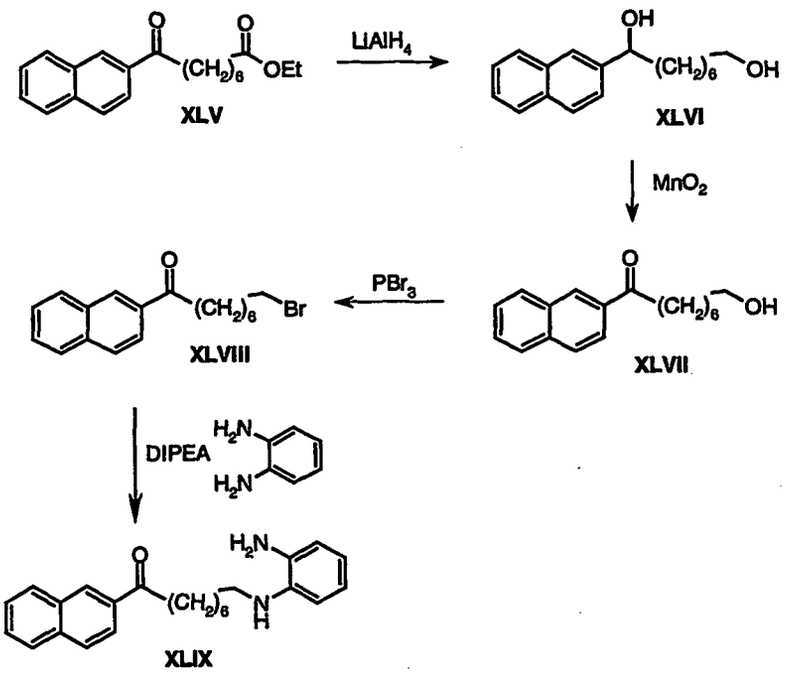


[0060] The compound of formula (4) (do not belong to the invention) is preferably prepared as described in the Examples.

[0061] The following synthesis example is for illustration purpose only.

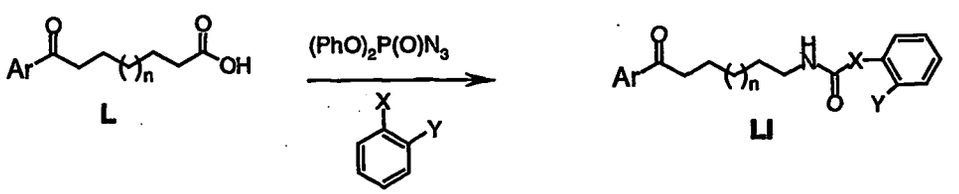
[0062] Compounds of formula (1), wherein W is -NH-Z are preferably prepared as outlined in Scheme 8. Reduction of the ketoester **XLV** affords the diol **XLVI,** which is oxidized selectively at the benzylic position with manganese **(IV)** oxide to give the ketone **XLVII.** The primary alcohol is substituted for the bromide group to afford **XLVIII** which is then converted to the aniline **XLIX.**

Scheme 8



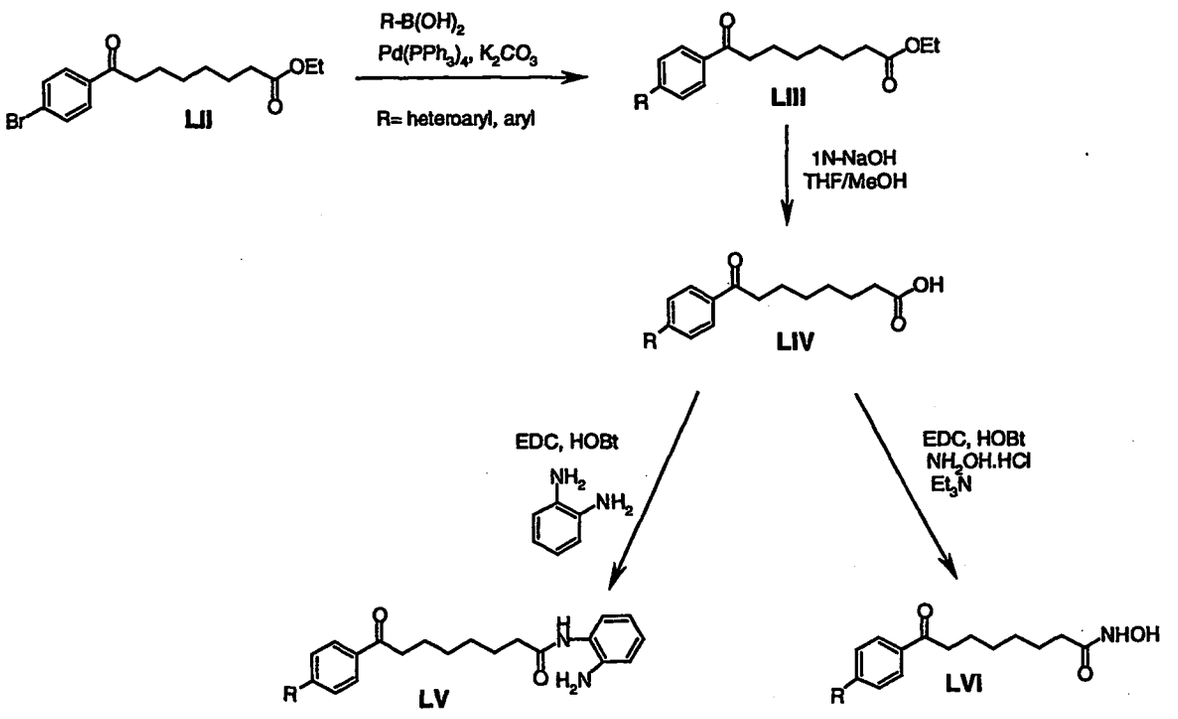
[0063] Carbamates (**LI,** X = O) and ureas (**LI**, X = NH) are preferably synthesized according to the route outlined in Scheme 9. Treatment of the carboxylic acid **L** with diphenylphosphoryl azide in the presence of triethylamine followed by *in situ* trapping of the resulting isocyanate with 1,2-phenylenediamine or 2-aminophenol affords the ureas **LI.** A similar procedure may be employed for the preparation of carbamates, by treating the isocyanate with pyridylcarbinol.

Scheme 9



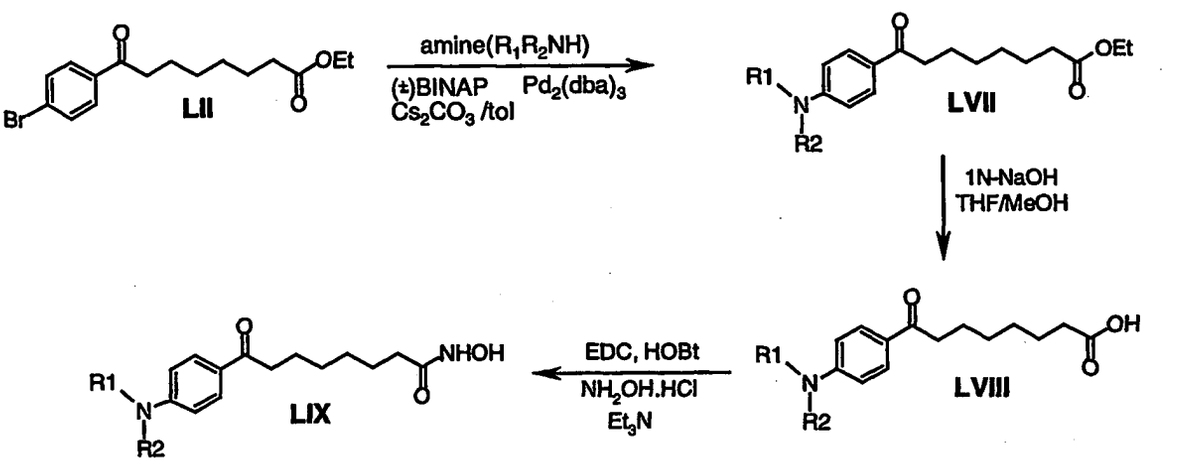
[0064] Compounds **LV** and **LVI,** wherein Cy is a biaryl moiety, may be prepared according to the synthetic route depicted in Scheme 10. The bromobenzoyl ester **LII** is treated with an heteroaryl- or arylboronic acids in presence of palladium(0) catalyst to afford esters **LIII.** Ester hydrolysis affords the acid **LIV,** which may be coupled with 1,2-phenylenediamine or with hydroxylamine to afford respectively the anilinyl amide **LV** or the hydroxamic acid **LVI.**

Scheme 10



[0065] Compounds **LIX,** wherein Cy is an aminophenyl moiety, preferably may be prepared according to the synthetic route depicted in Scheme 11. The bromobenzoyl ester **LII** is coupled with an amine in the presence of dibenzylacetone palladium and 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl to afford esters **LVII.** Ester hydrolysis affords the acid **LVIII,** which may be coupled with hydroxylamine to afford the hydroxamic acid **LIX.**

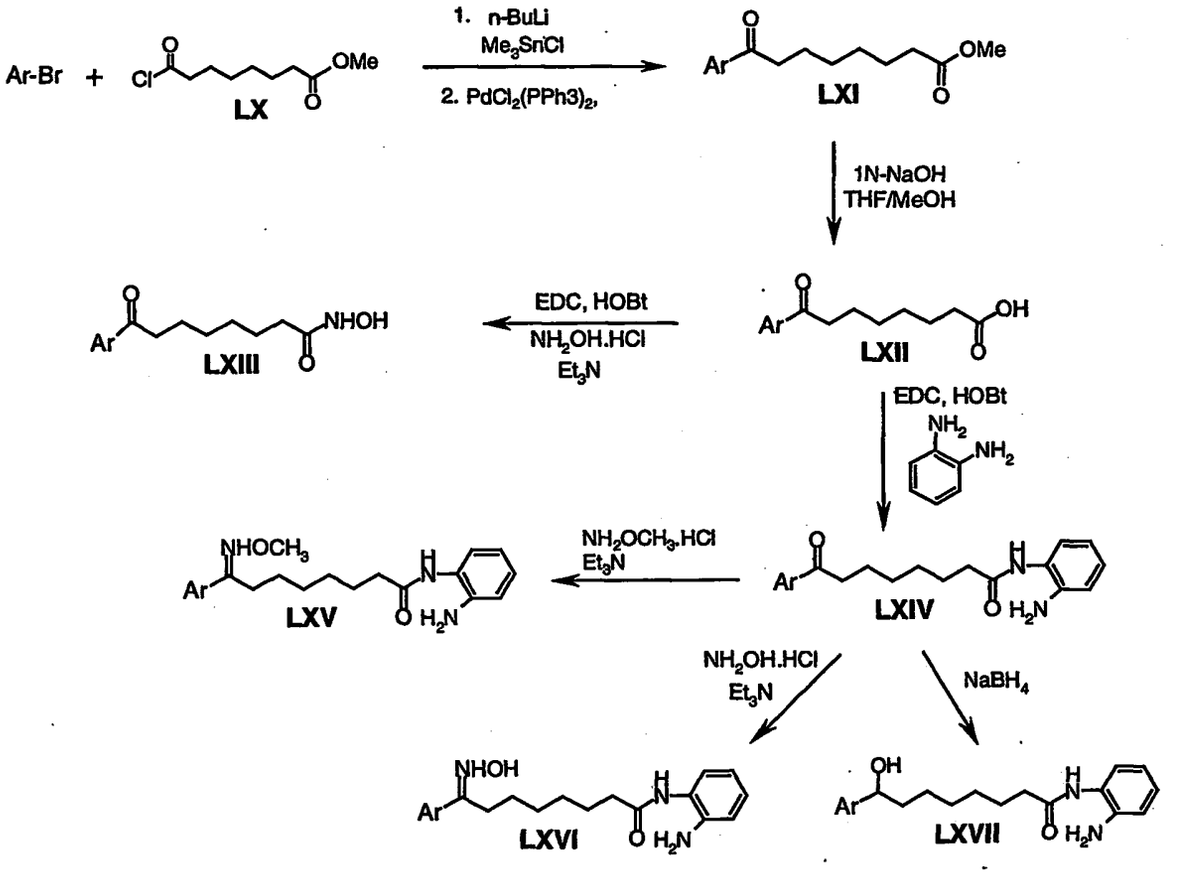
Scheme 11



[0066] Compounds **LXIII-LXVII** may be prepared according to the synthetic route depicted in Scheme 12. The aryl

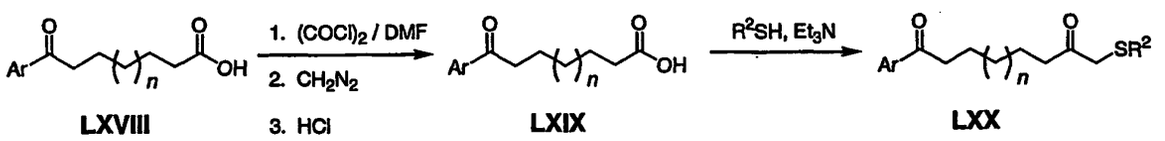
bromide is treated with n-butyllithium followed by trimethyltin chloride to give the aryltin compound, which may coupled with the acid chloride **LX** to afford the arylketoester **LXI.** Ester hydrolysis and the subsequent treatment of the acid **LXII** with hydroxylamine or 1,2-phenylenediamine affords respectively the hydroxamic acid **LXIII** or the anilinyl amide **LXIV.** The amides **LXIV** are easily converted to the oximes **LXV** and **LXVI.** Reduction of **LXIV** with sodium borohydride affords the alcohol **LXVI.**

Scheme 12



[0067] Compounds **LXX,** wherein W is -C(O)-CH_2SR^2, may be prepared according to the synthetic route depicted in Scheme 13. The carboxylic acid **LXVIII** is converted to α-chloromethylketone **LXIX** by the successive treatment of oxalyl chloride, diazomethane and hydrochloric acid. Replacement of chloride by a thiol in the presence of triethylamine affords the α-thiomethylketones **LXX.**

Scheme 13

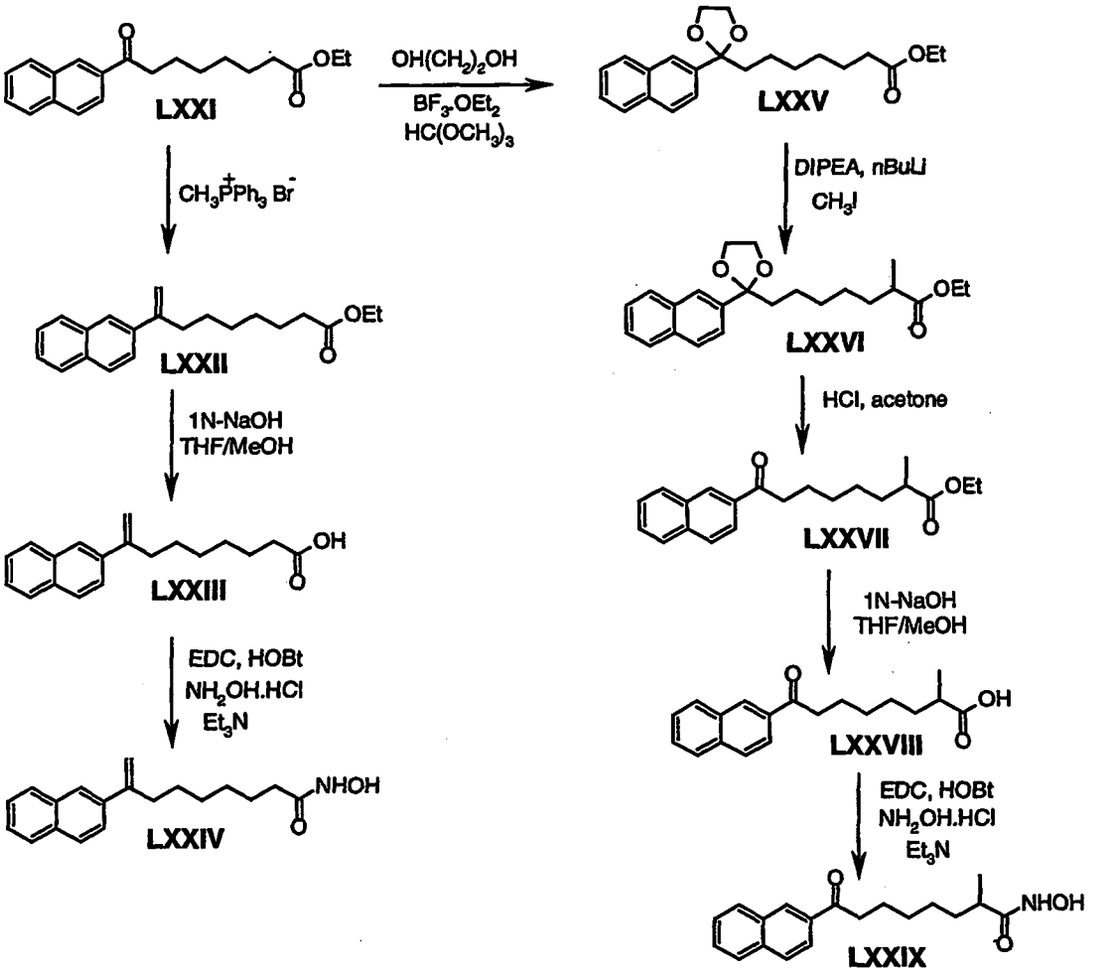


[0068] Compounds such as the compounds of formula **LXXIV** and **LXXIX** preferably may be prepared according to the route depicted in Scheme 14. Thus, the ketone **LXXI** is subjected to a Wittig reaction in the presence of methyl

phosphonium bromide to afford the ester **LXXII.** Ester hydrolysis affords the acid **LXXIII,** which may be coupled with hydroxylamine to afford the hydroxamic acid **LXXIV.**

[0069] Protection of the ketone **LXXI** by treatment with ethylene glycol in presence of borontrifluoride etherate and trimethyl orthoformate afford the acetal **LXXV.** α Methylation to **LXXVI** is then accomplished by treatment of **LXXV** with methyl iodide in the presence of lithium diisopropylethylamine. Deprotection of the acetal in acidic media, followed by the saponification of ester **LXXVII** and the subsequent conversion of the carboxylic acid **LXXVIII** to the hydroxamic acid afford **LXXIX.**

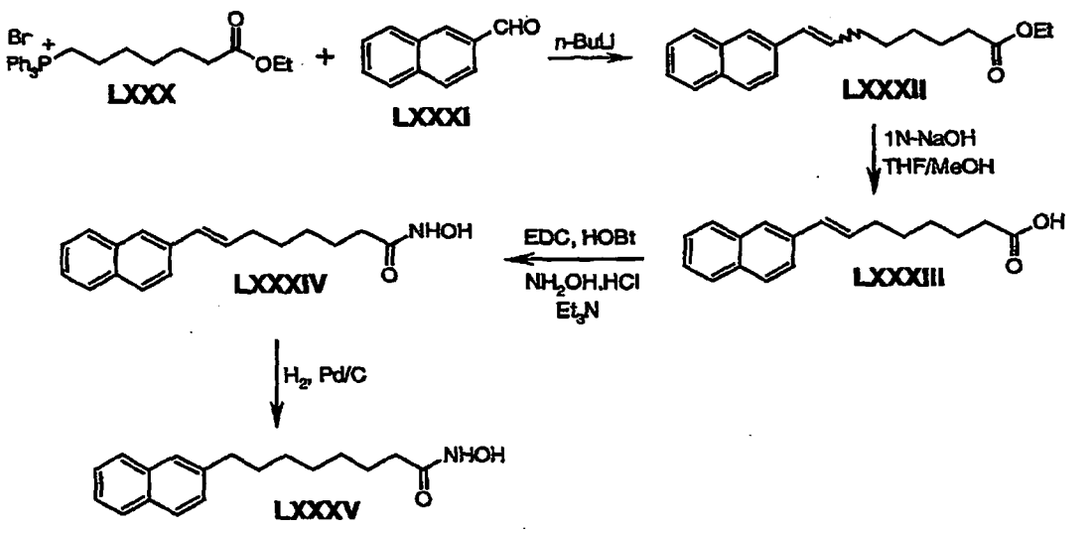
Scheme 14



[0070] The following synthesis example is for illustration purpose only.

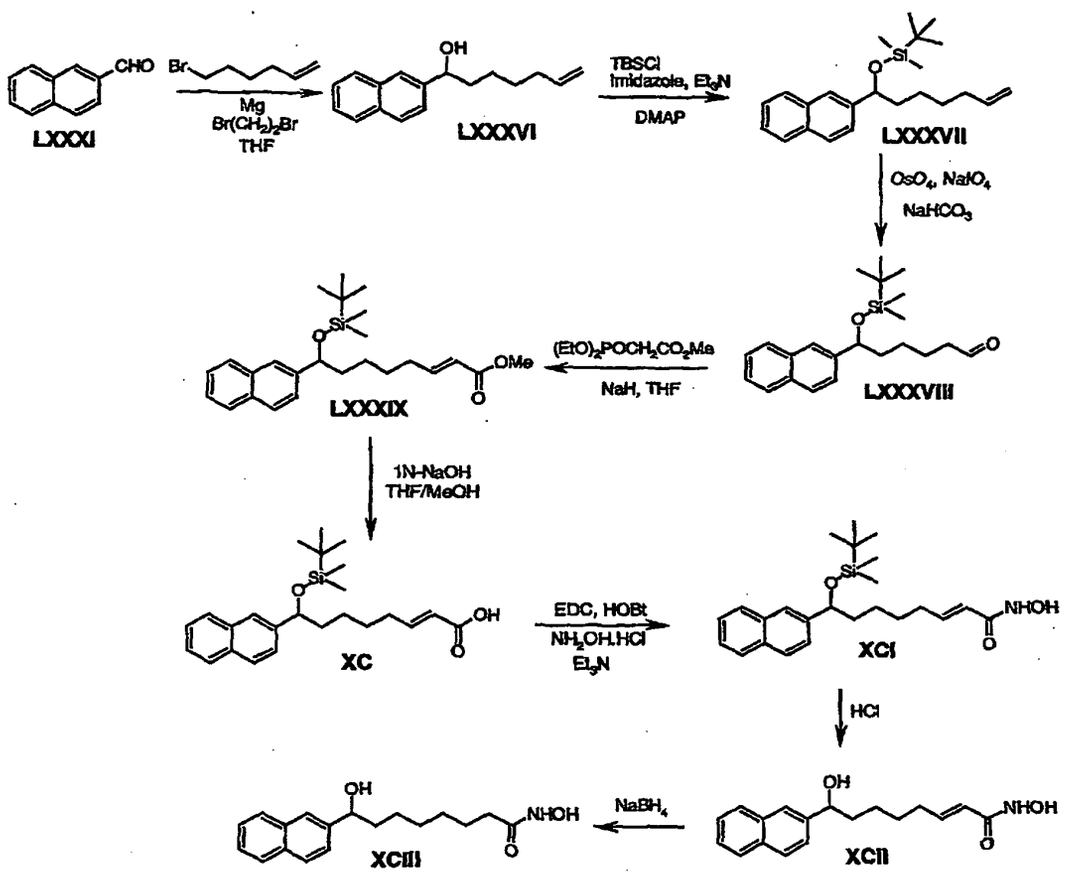
[0071] Compounds **LXXXIV** and **LXXXV** may be prepared according to the synthetic route depicted in Scheme 15. The aldehyde **LXXXI** was subjected to a Wittig reaction in the presence of the phosphonium bromide **LXXX to** afford a (E/Z) mixture of alkene **LXXXII.** Conversion of **LXXXII** to the hydroxamic acid **LXXXIV** is accomplished by a two steps procedure involving hydrolysis and coupling reaction with hydroxylamine. Reduction of **LXXXIV** by hydrogenation affords **LXXXV.**

Scheme 15



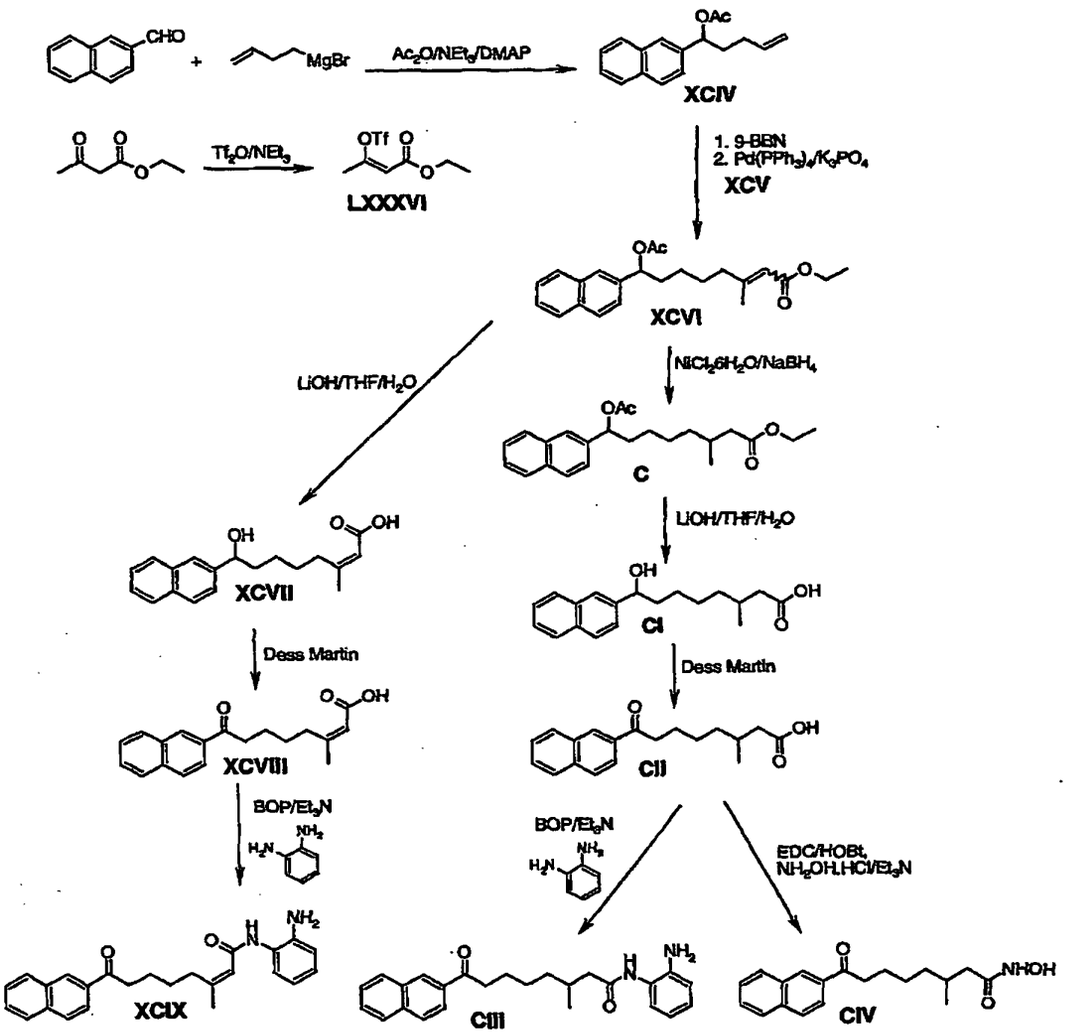
[0072] Compounds of formula (1) wherein X is CH(OH) may be prepared according to the synthetic route depicted for compounds **XCII** and **XCIII** in Scheme 16. The alcohol **LXXXVI,** prepared via a Grignard reaction of aldehyde **LXXXI** with 6-bromohexene, is protected by *tert*-butyldimethylsilyl group. Oxidative cleavage of olefin **LXXXVII** affords aldehyde **LXXXVIII,** which undergoes the Wittig reaction to give ester **LXXXIX.** Conversion of **LXXXIX** to the hydroxamic acid **XCI** is accomplished by procedure analogous to those described above for Scheme 1-3. Deprotection of silyl ether group of **XCI** affords **XCII,** which is reduced with sodium borohydride to give **XCIII.**

Scheme 16



[0073] Compounds of formula (1), wherein Y^1 is a substituted alkylene, preferably may be prepared as outlined for compounds **XCIX** (not belonging to the invention), **CIII** and **CIV** in Scheme 17. Hydroboration of the alkene **XCIV** with 9-BBN and the subsequent cross-coupling reaction with vinyl triflate **XCV** in the presence of palladium(0) catalyst affords the ester **XCVI.** Hydrolysis of ester **XCVI** followed by a Dess Martin oxidation gives the acid **XCVIII,** which is converted to the amide **XCIX.** Reduction of **XCVI** with sodium borohydride and nickel chloride affords the ester C. Conversion of **CII** to the anilinyl amide **CIII** and to the hydroxamic acid **CIV** is accomplished by procedure analogous to those described above for Scheme 1-3.

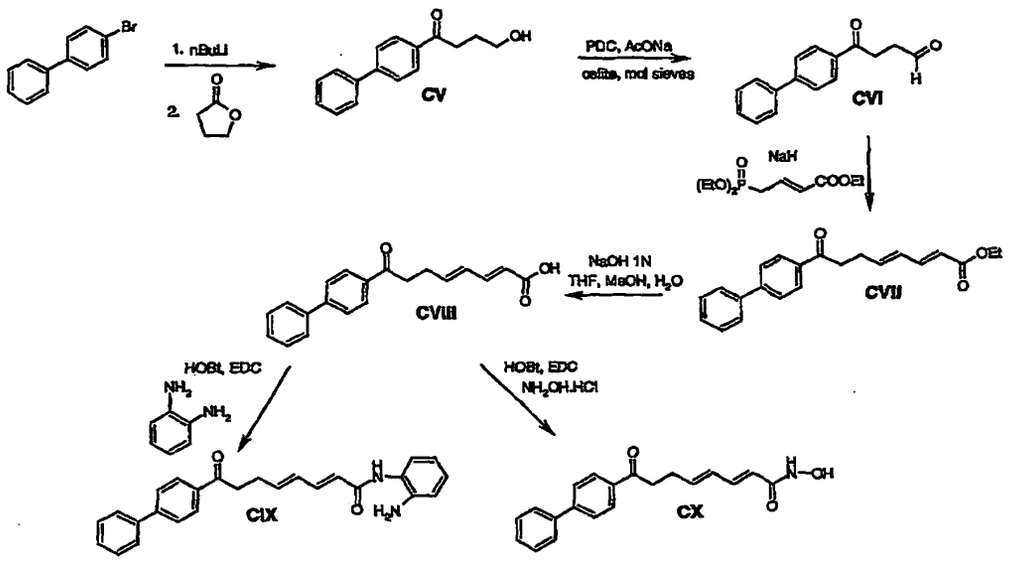
Scheme 17



[0074] The following synthesis example is for illustration purpose only.

[0075] Compounds **CIX** and **CX** may be prepared according to the synthetic route depicted in Scheme 18. The alcohol **CV** is prepared by treatment of bromobiphenyl with γ-butyrolactone in the presence of n-butyllithium. Oxidation of **CV** with pyridinium dichromate in the presence of sodium acetate affords the aldehyde **CVI,** which undergoes the Wittig reaction to give the diene ester **CVII.** Conversion of **CVII** to the anilinyl amide **CIX** and to the hydroxamic acid **CX** is accomplished-by procedure analogous to those described above for Scheme 1-3.

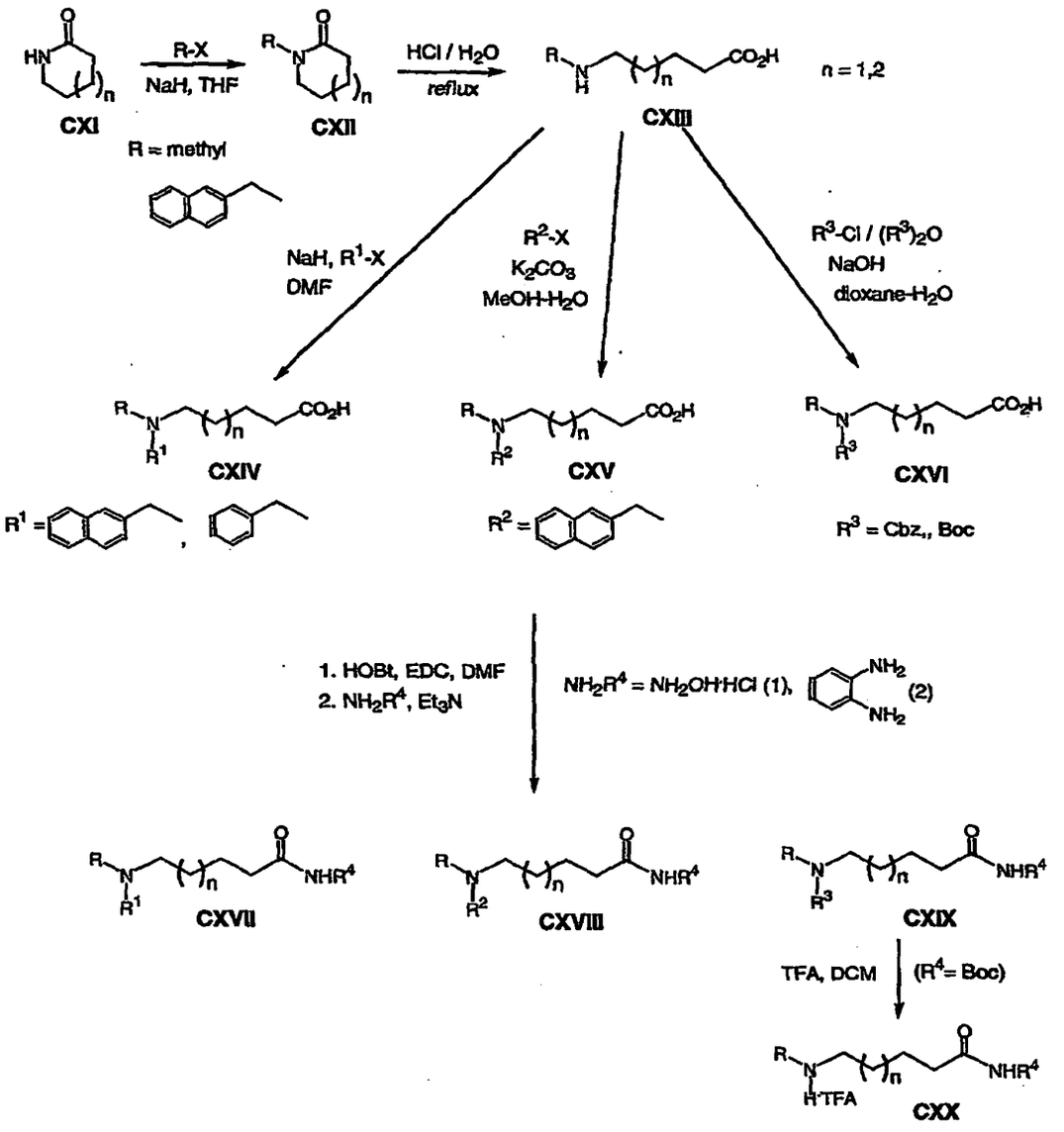
Scheme 18



[0076] The following synthesis example is for illustration purpose only.

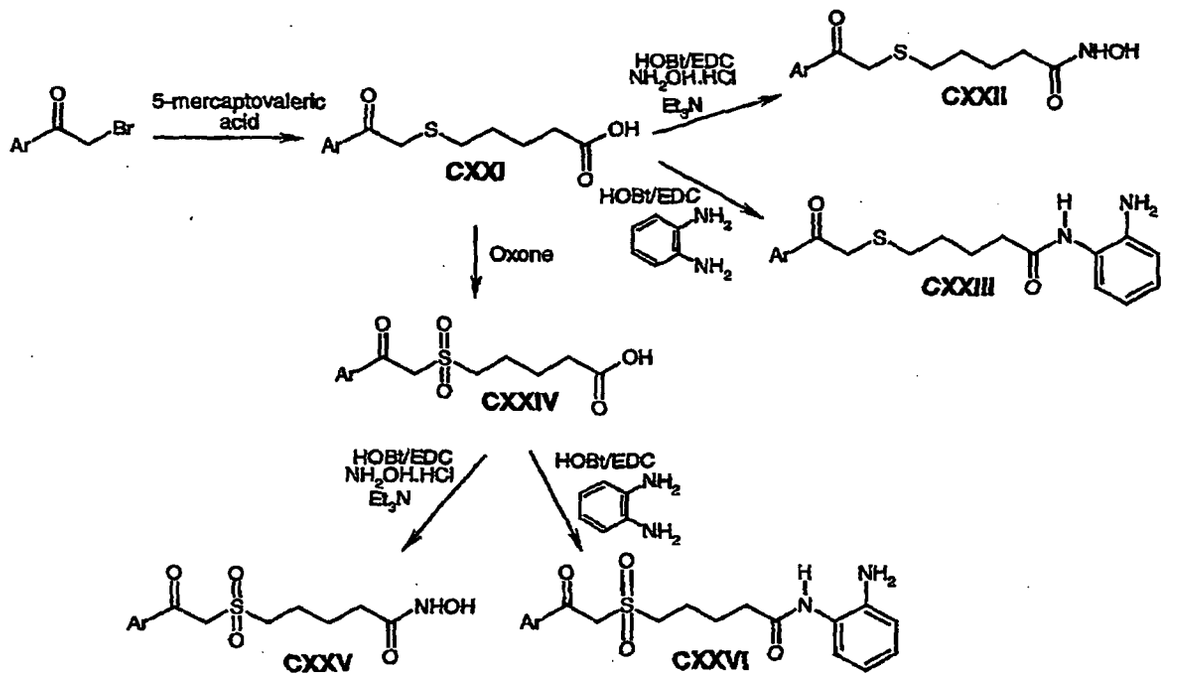
[0077] Comopounds of formula (2), wherein one carbon atom in the linear chain connecting Cy and W is replaced by NR^3, preferably may be prepared as outlined for compounds **CXVII-CXX** in Scheme 19. The lactone **CXI** is *N*-alkylated with methyl iodide or 2-bromomethylnaphthalene in the presence of a base to afford **CXII,** which is hydrolyzed under acid condition to give the amino acid **CXIII.** A subsequent *N*-alkylation or *N*-acylation affords respectively the tertiary amine **CXIIV** and **CXV** or the carbamate **CXVI.** Conversion of **CXIV, CXV** and **CXVI** to the anilinyl amide or hydroxamic acid, respectively, **CXVII, CXVIII** and **CXIX** is accomplished by procedure analogous to those described above for Scheme 1-3. Deprotection of **CXIX** using trifluoroacetic acid affords **CXX.**

Scheme 19



[0078] Compounds of formula (1), wherein one carbon atom in the linear chain connecting X and W is replaced by S (O), preferably may be prepared as outlined in Scheme 20. The acid **CXXI** is prepared by treatment of 5-mercaptovaleric acid and the aryl ketone in the presence of a base. The oxidation of the sulfide of **CXXI** with oxone affords the acid **CXXIV.** Conversion of **CXXI** and **CXXIV** respectively to the anilinyl amide **CXXIII** and **CXXVI** and to the hydroxamic acid **CXXII** and **CXXV** is accomplished by the procedures analogous to those described above for Scheme 1-3.

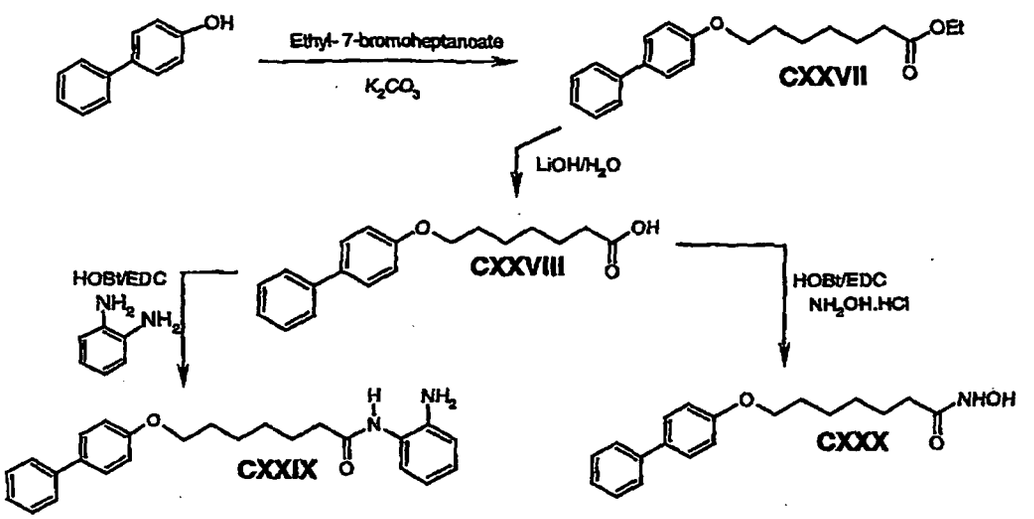
Scheme 20



[0079] The following synthesis example is for illustration purpose only.

[0080] Compounds of formula (2), wherein one carbon atom in the linear chain connecting Cy and W is replaced by an oxygen atom, preferably may be prepared as outlined for compounds **CXXIX** and **CXXX** in Scheme 21. The ester **CXXVII** is prepared by treatment of ethyl-7-bromoheptanoate and the 4-phenylphenol in the presence of a base. Hydrolysis of ester and the subsequent conversion of the carboxylic acid **CXXVIII** to the anilinyl amide and hydroxamic acid affords respectively **CXXIX** and **CXXX.**

Scheme 21

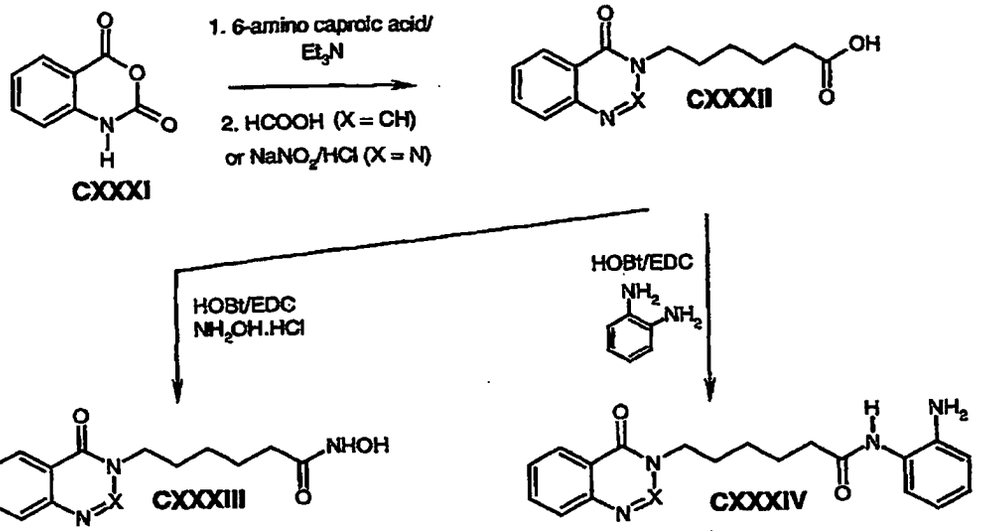


[0081] The following synthesis example is for illustration purpose only.

[0082] Compounds of formula (2), wherein Cy is an N-linked heterocycle, preferably may be prepared according to routes analogous to those depicted in Schemes 22-24. Treatment of 6-aminocaproic acid and the anhydride **CXXXI** in

the presence of a base, followed by a reflux in formic acid or diazotization afford the acid **CXXXII** (wherein X=CH or X=N respectively). The conversion of the carboxylic acid **CXXXII** to the hydroxamic acid and anilinyl amide afford respectively **CXXXIII** and **CXXXIV.**

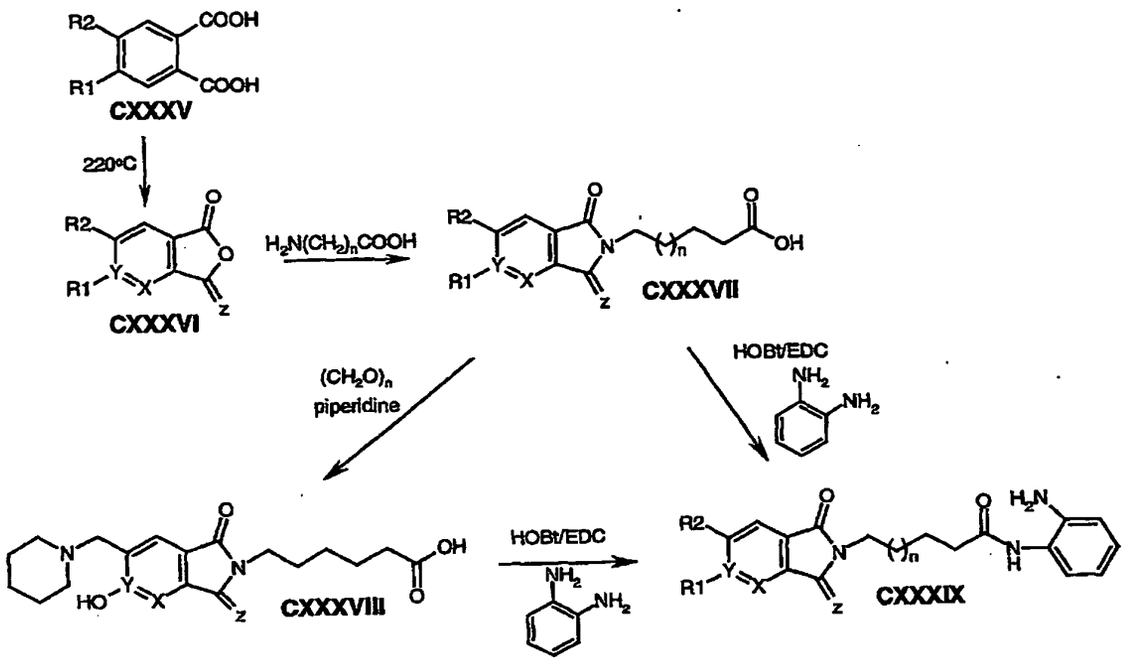
Scheme 22



[0083] The following example is for illustration purpose only.

[0084] The anhydride **CXXXVI** is prepared by heating of the diacid **CXXXV**, as shown in Scheme 23. The treatment of the anhydride **CXXXVI** with an amino acid in the presence of a base affords the acid **CXXXVII**. A subsequent treatment of the acid **CXXXVII** with 1-methylpiperidine in the presence of paraformaldehyde affords the acid **CXXXVIII.** The conversion of the carboxylic acid **CXXXVII** or **CXXXVIII** to the hydroxamic acid and anilinyl amide afford respectively **CXXXIX.**

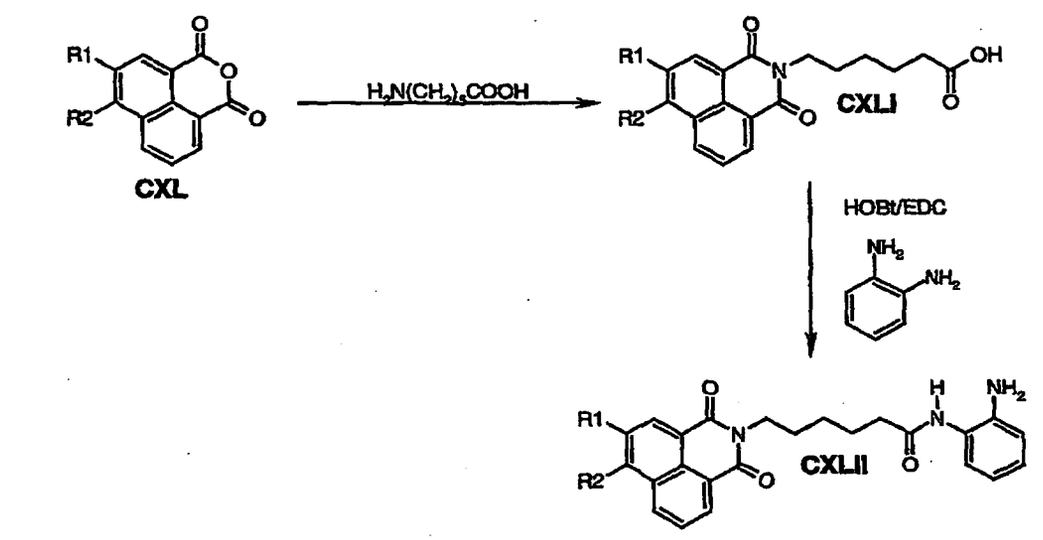
Scheme 23



[0085] The following example is for illustration purpose only.

[0086] Treatment of the anhydride CXL with an amino acid in the presence of a base affords the add **CXLI**, as shown, in Scheme 24. The conversion of the carboxylic acid **CXLI** to the anilinyl amide then affords **CXLIL**.

Scheme 24



Pharmaceutical Compositions

[0087] In a second aspect, the invention provides a pharmaceutical composition comprising an inhibitor of histone deacetylase represented by formula (1) or (5) and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any

route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain preferred embodiments, compounds of the invention are administered intravenously in a hospital setting, In certain other preferred embodiments, administration may preferably be by the oral route.

[0088] The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient (s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, *e.g.*, Remington's Pharmceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, PA, 1990.

Inhibition of Histone Deacetylase

[0089] Inhibiting histone deacetylase in a cell comprises contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase represented by any one of formulae (1)-(7).

[0090] Measurement of the enzymatic activity of a histone deacetylase can be achieved using known methodologies. For example, Yoshida et al., J. Biol. Chem., 265: 17174-17179 (1990), describes the assessment of histone deacetylase enzymatic activity by the detection of acetylated histones in trichostatin A treated cells. Taunton et al., Science, 272: 408-411 (1996), similarly describes methods to measure histone deacetylase enzymatic activity using endogenous and recombinant HDAC-1.

[0091] The histone deacetylase inhibitor can interact with and reduce the activity of all histone deacetylases in the cell. The histone deacetylase inhibitor can also interact with and reduces the activity of fewer than all histone deacetylases in the cell. For example, the inhibitor can interact with and reduce the activity of one histone deacetylase (*e.g.*, HDAC-1), but can not interact with or reduce the activities of other histone deacetylases (*e.g.*, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8). As discussed below, certain histone deacetylase inhibitors are those that interact with and reduce the enzymatic activity of a histone deacetylase that is involved in tumorigenesis. Certain other histone deacetylase inhibitors interact with and reduce the enzymatic activity of a fungal histone deacetylase.

[0092] Inhibiting histone deacetylase in a cell can cause an inhibition of cell proliferation of the contacted cells. The phrase "inhibiting cell proliferation" is used to denote an ability of an inhibitor of histone deacetylase to retard the growth of cells contacted with the inhibitor as compared to cells not contacted. An assessment of cell proliferation can be made by counting contacted and non-contacted cells using a Coulter Cell Counter (Coulter; Miami, FL) or a hemacytometer. Where the cells are in a solid growth (*e.g.*, a solid tumor or organ), such an assessment of cell proliferation can be made by measuring the growth with calipers and comparing the size of the growth of contacted cells with non-contacted cells.

[0093] Growth of cells contacted with the inhibitor can be retarded by at least 50% as compared to growth of non-contacted cells. Cell proliferation can be inhibited by 100% (*i.e.,* the contacted cells do not increase in number or size). The phrase "inhibiting cell proliferation" can include a reduction in the number of contacted cells, as compared to non-contacted cells. Thus, an inhibitor of histone deacetylase according to the invention that inhibits cell proliferation in a contacted cell may induce the contacted cell to undergo growth retardation, to undergo growth arrest, to undergo programmed cell death (*i.e.*, to apoptose), or to undergo necrotic cell death.

[0094] The cell proliferation inhibiting ability of the histone deacetylase inhibitors according to the invention allows the synchronization of a population of asynchronously growing cells. For example, the histone deacetylase inhibitors of the invention may be used to arrest a population of non-neoplastic cells grown *in vitro* in the G1 or G2 phase of the cell cycle. Such synchronization allows, for example, the identification of gene and/or gene products expressed during the G1 or G2 phase of the cell cycle. Such a synchronization of cultured cells may also be useful for testing the efficacy of a new transfection protocol, where transfection efficiency varies and is dependent upon the particular cell cycle phase of the cell to be transfected. Use of the histone deacetylase inhibitors of the invention allows the synchronization of a population of cells, thereby aiding detection of enhanced transfection efficiency.

[0095] In some preferred embodiments, the contacted cell is a neoplastic cell. The term "neoplastic cell" is used to denote a cell that shows aberrant cell growth. Preferably, the aberrant cell growth of a neoplastic cell is increased cell growth. A neoplastic cell may be a hyperplastic cell, a cell that shows a lack of contact inhibition of growth *in vitro,* a benign tumor cell that is incapable of metastasis *in vivo*, or a cancer cell that is capable of metastasis *in vivo* and that may recur after attempted removal. The term "tumorigenesis" is used to denote the induction of cell proliferation that leads to the development of a neoplastic growth. In some embodiments, the histone deacetylase inhibitor induces cell differentiation in the contacted cell. Thus, a neoplastic cell, when contacted with an inhibitor of histone deacetylase may be induced to differentiate, resulting in the production of a daughter cell that is phylogenetically more advanced than the contacted cell.

[0096] In some preferred embodiments, the contacted cell is in an animal. Thus, the invention relates to the use of histone deacetylase for the manufacture of a medicament for treating a cell proliferative disease or condition in an animal,

comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably, the animal is a mammal, more preferably a domesticated mammal. Most preferably, the animal is a human.

[0097] The term "cell proliferative disease or condition" is meant to refer to any condition characterized by aberrant cell growth, preferably abnormally increased cellular proliferation. Examples of such cell proliferative diseases or conditions include, but arc not limited to, cancer, restenosis, and psoriasis. In particularly preferred embodiments, the invention provides a use for the manufacture of a medicament for inhibiting neoplastic cell proliferation in an animal comprising administering to an animal having at least one neoplastic cell present in its body a therapeutically effective amount of a histone deacetylase inhibitor of the invention.

[0098] It is contemplated that some compounds of the invention have inhibitory activity against a histone deacetylase from a protozoal source. Thus, the invention also relates to the use of histone deacetylase for the manufacture of a medicament for treating or preventing a protozoal disease or infection, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a protozoal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly, human histone deacetylases.

[0099] The present invention further relates to the use of histone deacetylase for the manufacture of a medicament for treating a fungal disease or infection comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a fungal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

[0100] The term "therapeutically effective amount" is meant to denote a dosage sufficient to cause inhibition of histone deacetylase activity in the cells of the subject, or a dosage sufficient to inhibit cell proliferation or to induce cell differentiation in the subject. Administration may be by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain particularly preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

[0101] When administered systemically, the histone deacetylase inhibitor is preferably administered at a sufficient dosage to attain a blood level of the inhibitor from about 0.01 μM to about 100 μM, more preferably from about 0.05 μM to about 50 μM, still more preferably from about 0.1 μM to about 25 μM, and still yet more preferably from about 0.5 μM to about 25 μM ; For localized administration, much lower concentrations than this may be effective, and much higher concentrations may be tolerated. One of skill in the art will appreciate that the dosage of histone deacetylase inhibitor necessary to produce a therapeutic effect may vary considerably depending on the tissue, organ, or the particular animal or patient to be treated.

[0102] In certain preferred embodiments of the third aspect of the invention, the use further comprises contacting the cell with an antisense oligonucleotide that inhibits the expression of a histone deacetylase. The combined use of a nucleic acid level inhibitor (*i.e*., antisense oligonucleotide) and a protein level inhibitor (*i.e*., inhibitor of histone deacetylase enzyme activity) results in an improved inhibitory effect, thereby reducing the amounts of the inhibitors required to obtain a given inhibitory effect as compared to the amounts necessary when either is used individually. The antisense oligonuncleotides according to this aspect of the invention are complementary to regions of RNA or double-stranded DNA that encode HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and/or HDAC-8 (see *e.g*., GenBank Accession Number U50079 for HDAC-1, GenBank Accession Number U31814 for HDAC-2, and GenBank Accession Number U75697 for HDAC-3).

[0103] For purposes of the invention, the term "oligonucleotide" includes polymers of two or more deoxyribonucleosides, ribonucleosides, or 2'-O-substituted ribonucleoside residues, or any combination thereof. Preferably, such oligonucleotides have from about 6 to about 100 nucleoside residues, more preferably from about 8 to about 50 nucleoside residues, and most preferably from about 12 to about 30 nucleoside residues. The nucleoside residues may be coupled to each other by any of the numerous known internucleoside linkages. Such internucleoside linkages include without limitation phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate and sulfone internucleoside linkages. In certain preferred embodiments, these internucleoside linkages may be phosphodiester, phosphotriester, phosphorothioate, or phosphoramidate linkages, or combinations thereof. The term oligonucleotide also encompasses such polymers having chemically modified bases or sugars and/ or having additional substituents, including without limitation lipophilic groups, intercalating agents, diamines and adamantane. For purposes of the invention the term "2'-O substituted" means substitution of the 2' position of the pentose moiety with an - O-lower alkyl group containing 1-6 saturated or unsaturated carbon atoms, or with an -O-aryl or allyl group having 2-6 carbon atoms, wherein such alkyl, aryl or allyl group may be

unsubstituted or may be substituted, *e.g.*, with halo, hydroxy, trifluoromethyl, cyano, nitro, acyl, acyloxy, alkoxy, carboxyl, carbalkoxyl, or amino groups; or such 2' substitution may be with a hydroxy group (to produce a ribonucleoside), an amino or a halo group, but not with a 2'-H group.

[0104] Particularly preferred antisense oligonucleotides utilized in this aspect of the invention include chimeric oligonucleotides and hybrid oligonucleotides.

[0105] For purposes of the invention, a "chimeric oligonucleotide" refers to an oligonucleotide having more than one type of internucleoside linkage. One preferred example of such a chimeric oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region, preferably comprising from about 2 to about 12 nucleotides, and an alkylphosphonate or alkylphosphonothioate region (see *e.g.*, Pederson et al. U.S. Patent Nos. 5,635,377 and 5,366,878). Preferably, such chimeric oligonucleotides contain at least three consecutive internucleoside linkages selected from phosphodiester and phosphorothioate linkages, or combinations thereof.

[0106] For purposes of the invention, a "hybrid oligonucleotide" refers to an oligonucleotide having more than one type of nucleoside. One preferred example of such a hybrid oligonucleotide comprises a ribonucleotide or 2'-O-substituted ribonucleotide region, preferably comprising from about 2 to about 12 2'-O-substituted nucleotides, and a deoxyribonucleotide region. Preferably, such a hybrid oligonucleotide will contain at least three consecutive deoxyribonucleosides and will also contain ribonucleosides, 2'-O-substituted ribonucleosides, or combinations thereof (see *e.g.*, Metelev and Agrawal, U.S. Patent No. 5,652,355).

[0107] The exact nucleotide sequence and chemical structure of an antisense oligonucleotide utilized in the invention can be varied, so long as the oligonucleotide retains its ability to inhibit expression of the gene of interest. This is readily determined by testing whether the particular antisense oligonucleotide is active by quantitating the mRNA encoding a product of the gene, or in a Western blotting analysis assay for the product of the gene, or in an activity assay for an enzymatically active gene product, or in a soft agar growth assay, or in a reporter gene construct assay, or an *in vivo* tumor growth assay, all of which are described in detail in this specification or in Ramchandani et al. (1997) Proc. Natl. Acad. Sci. USA 94: 684-689.

[0108] Antisense oligonucleotides utilized in the invention may conveniently be synthesized on a suitable solid support using well known chemical approaches, including H-phosphonate chemistry, phosphoramidite chemistry, or a combination of H-phosphonate chemistry and phosphoramidite chemistry (*i.e.*, H-phosphonate chemistry for some cycles and phosphoramidite chemistry for other cycles). Suitable solid supports include any of the standard solid supports used for solid phase oligonucleotide synthesis, such as controlled-pore glass (CPG) (see, *e.g.*, Pon, RT. (1993) Methods in Molec. Biol. 20: 465-496).

[0109] Particularly preferred oligonucleotides have nucleotide sequences of from about 13 to about 35 nucleotides which include the nucleotide sequences shown in Table 1. Yet additional particularly preferred oligonucleotides have nucleotide sequences of from about 15 to about 26 nucleotides of the nucleotide sequences shown in Table 1.

Table 1

Oligo	Target	Accession Number	Nucleotide Position	Sequence	position within Gene
HDAC1 AS1	Human HDAC1	U50079	1585-1604	5'-GAAACGTGAGGGACTCAGCA-3'	3'-UTR
HDAC1 AS2	Human HDAC1	U50079	1565-1584	5'-GGAAGCCAGAGCTGGAGAGG-3'	3'-UTR
HDAC1 MM	Human HDAC1	U50079	1585-1604	5'-GTTAGGTGAGGCACTGAGGA-3'	3'-UTR
HDAC2 AS	Human HDAC2	U31814	1643-1622	5'-GCTGAGCTGTTCTGATTTGG3'	3'-UTR
HDAC2 MM	Human HDAC2	U31814	1643-1622	5'-CGTGAGCACTTCTCATTTCC-3'	3'-UTR
HDAC3 AS	Human HDAC3	AF039703	1276-1295	5'-CGCTTTCCTTGTCATTGACA-3'	3'-UTR
HDAC3 MM	Human HDAC3	AF039703	1276-1295	5'-GCCTTTCCTACTCATTGTGT-3'	3'-UTR

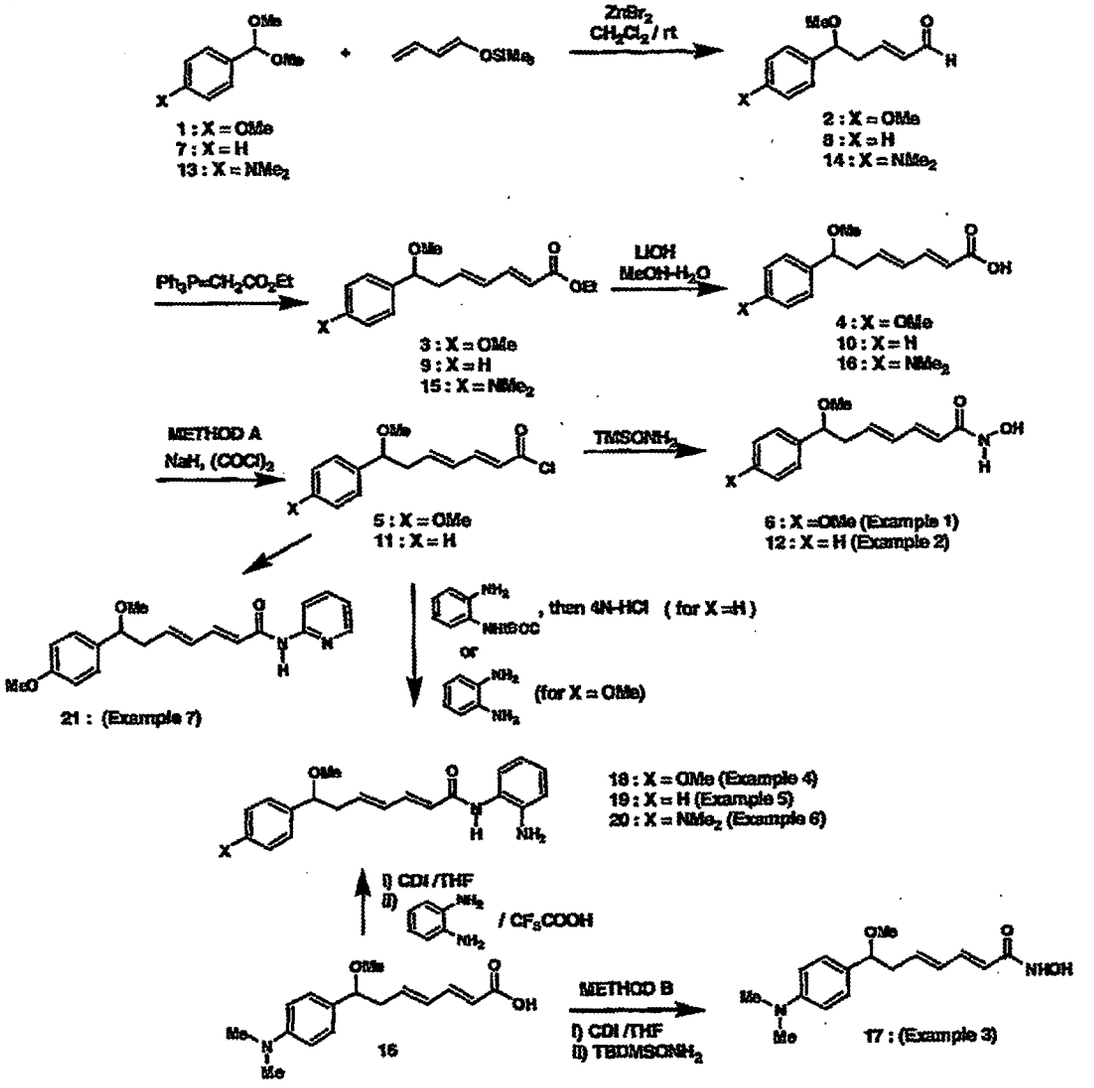
(continued)

Oligo	Target	Accession Number	Nucleotide Position	Sequence	position within Gene
HDAC4 AS1	Human HDAC4	AB006626	514-33	5-GCTGCCTGCCGTGCCCACCC-3'	5'-UTR
HDAC4 MM1	Human HDAC4	AB006626	514-33	5'-CGTGCCTGCGCTGCCCACGG-3'	5'-UTR
HDAC4 AS2	Human HDAC4	AB006626	7710-29	5'-TACAGTCCATGCAACCTCCA-3'	3'-UTR
HDAC4 MM4	Human HDAC4	AB006626	7710-29	5'-ATCAGTCCAACCAACCTCGT-3'	3'-UTR
HDAC5 AS	Human HDAC5	AF039691	2663-2682	5'-CTTCGGTCTCACCTGCTTGG-3'	3'-UTR
HDAC6 AS	Human HDAC6	AJ011972	3791-3810	5'-CAGGCTGGAATGAGCTACAG-3'	3'-UTR
HDAC6 MM	Human HDAC6	AJ011972	3791-3810	5'-GACGCTGCAATCAGGTAGAC-3'	3'-UTR
HDAC7 AS	Human HDAC7	AF239243	2896-2915	5'-CTTCAGCCAGGATGCCCACA-3'	3'-UTR
HDAC8 AS1	Human HDAC8	AF230097	51-70	5'-CTCCGGCTCCTCCATCTTCC-3'	5'-UTR
HDAC8 AS2	Human HDAC8	AF230097	1328-1347	5'-AGCCAGCTGCCACTTGATGC-3'	3'-UTR

[0110] The following examples are intended to further illustrate certain preferred embodiments of the invention, and are not intended to limit the scope of the invention.

EXAMPLES

[0111]



[0112] Examples 1 to 7 are for illustration purpose only.

Example 1:

***N*-Hydroxy-7-methoxy-7-(4-methoxyphenyl)-2,4-heptadienamide (6)**

Step 1: 5-Methoxy-5-(4-methoxyphenyl)]-2-pentanal (**2**)

[0113] To a stirred solution of *p*-anisaldehyde dimethyl acetal (**1**) (1.82g, 10 mmol) in dry CH_2Cl_2 (60 mL) at rt was added 1-trimethylsilyloxy-1,3-butadiene (1.42 g,10 mmol) followed by catalytic amount of anhydrous $ZnBr_2$ (25 mg). After being stirred for 5 h at rt, the reaction was quenched with water (20 mL). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product by flash silica gel chromatography (25% ethyl acetate in hexane) afforded the desired aldehyde **2** (1.15 g, 61% yield) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 6.81 (dt, J = 15.6,6.9 Hz, 1H), 6.12 (ddt, J =15.6, 7.8, 1.5Hz,1H), 4.23 (dd, J = 8.1, 5.1 Hz,1H), 3.81 (s, 3H), 3.20 (s, 3H), 2.78 (m, 1H), 2.65 (m,1H).

Step 2: Ethyl-7-methoxy-7(4-methoxyphenyl)-2,4-heptadienoate (**3**)

[0114] A mixture of aldehyde **2** (1.13 g, 5.14 mmol) and ethyl (triphenylphosphoranylidene)acetate (2.15 g, 6.16 mmol) in CH_2Cl_2 (25 mL) was heated at reflux for 5 h under N_2. After removal of the solvent under reduced pressure, the crude product obtained was purified by flash silica gel chromatography (10% ethyl acetate in hexane) to give the title compound **3** (1.10 g, 74% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 3H), 6.88 (d, J =8.7 Hz, 2H), 5.99-6.21 (m, 2H), 5.76 (d, J = 15.3Hz, 1H), 4.18 (q, J =7.2 Hz, 2H), 4.13 (dd, J =8.4, 6.0 Hz, 1H), 3.81 (s, 3 H), 3.18 (s, 3H), 2.64 (m, 1H), 2.48 (m, 1H), 1.28 (t, J = 7.2Hz, 3H).

Step 3: 7 Methoxy-7-(4-methoxyphenyl)-2,4-heptadienoic acid (**4**)

[0115] To a stirred solution of diene ester **3** (0.36g, 1.24mmol) in methanol (10 mL) at rt was added aqueous LiOH 0.5 N solution (3.4 mL, 1.7mmol). After being stirred at 40 ˚C for 16 h, methanol was removed under reduced pressure and the resulting aqueous solution was acidified with 3N HCl (pH = ca. 4), extracted with ethyl acetate (25 × 3 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give the desired carboxylic acid **4** (0.30 g, 92% yield). Without further purification, the crude product was used in the next step: ^{1}H NMR (300 MHz, CD_3OD): δ 7.23 (d, J = 9.0 Hz, 2H), 7.00 (dd, J = 15.3,10.5 Hz, 1H), 6.93 (d, J = 9.0 Hz, 2H), 6.17 (dd, J = 15.3,10.5 Hz, 1H); 5.93 (dd, J = 15.3,10.5 Hz, 1H), 5.85 (d, J = 15.3 Hz,1H), 4.20 (br t, J =6.6 Hz, 1H), 3.82 (s, 3 H), 3.20 (s, 3H), 2.61 (m. 1H), 2.48 (m, 1H).

Method A

Step 4: 7-Methoxy-7-(4-methoxyphenl)-2,4-heptadienoic acid chloride (**5**)

[0116] To a suspension of 60% NaH (0.059 g,1.47 mmol) washed previously with dry pentane (2 × 5 mL) in dry benzene (5 mL) at 5 ˚C was added dropwise a solution of carboxylic acid **4** (0.30 g,1.14 mmol) in dry benzene (5 mL) via cannula. After 20 min, oxalyl chloride (117 μL, 1.34 mmol) was added via microsyringe, and then the reaction mixture was allowed to warm to rt over 30 min. After stirring for an additional 1.5 h at rt, the mixture was filtered and the filtrate was concentrated under reduced pressure to give the desired acid chloride **5** in 93 % yield as a red-orange oil. Without further purification, this crude product was used in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (dd, J = 15.3, 10.5 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.30 (m, 2H), 5.98 (d, J = 15.3 Hz, 1H), 4.18 (dd, J = 7.5, 4.8 Hz, 1H), 3.82 (s, 3 H), 3.20 (s, 3H), 2.61 (m, 1H), 2.48 (m, 1H).

Step 5: *N*-Hydroxy-7-methoxy-7-(4-methoxyphenyl)-2,4-heptadienamide-(**6**)

[0117] To a stirred solution of trimethylsilyloxy hydroxylamine (132 μL, 1.08 mmol) and *N*-methylmorpholine (44 μL, 0.40 mmol) in CH_2Cl_2 (5 mL) at 0 ˚C was added dropwise a solution of acid chloride **5** (101 mg, 0.36 mmol) via cannula. The reaction mixture was stirred for 1 h, and then was allowed to warm to rt over 1 h. After being stirred for an additional 1 h, the reaction mixture was diluted with $CHCl_3$: MeOH (20 mL: 1 mL), washed with saturated $NaHCO_3$ solution and then water, and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash silica gel chromatography (5-10% MeOH in $CHCl_3$) gave the desired hydroxamic acid **6** (30 mg, 30%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 3H), 6.87 (d, J = 7.5 Hz, 2H), 5.60- 6.20 (m, 3H), 4.10 (m,1H), 3.79 (s, 3 H), 3.16 (s, 3H), 2.61 (m, 1H), 2.43 (m,1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 41.6,
55.2, 56.4, 82.7, 113.8, 117.9, 127.8, 130.4, 133.1, 139.3, 141.7, 159.2, 165.5.

Example 2:

***N*-Hydroxy-7-methoxy-7-phenyl-2,4-heptadienamide (12)**

Step 1: 5-Methoxy-5-phenyl-2-pentanal (**8**)

[0118] Following a procedure analogous to that described in Example 1, step1, but substituting benzaldehyde dimethyl acetal **7** for *p*-anisaldehyde dimethyl acetal **1**, the title compound was obtained in 60% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (d, J = 8.1 Hz, 1H), 7.31 (m, 5H), 6.83 (dt, J =15.6, 7.2 Hz, 1H), 6.12 (ddt, J =15.6, 8.1,1.5 Hz, 1H), 4.30 (dd, J = 8.1,4.8 Hz, 1H), 3.24 (s, 3H), 2.79 (m, 1H), 2.67 (m, 1H).

Step 2: Ethyl-7-methoxy-7-phenyl-2,4- heptadienoate (**9**)

[0119] Following a procedure analogous to that described in Example 1, step 2, but substituting aldehyde **8** for aldehyde

2, the title compound was obtained in 63% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 6H), 6.11 (m, 2H), 5.76 (d,J = 15.3 Hz, 1H), 4.18 (q, J =7.2 Hz, 2H), 4.16(dd,J =7.5,5.4 Hz, 1H), 3.21(s, 3 H), 2.64 (m,1H), 2.50 (m,1H), 1.28 (t, J = 7.2 Hz, 3H).

Step 3: 7-Methoxy-7-phenyl-2,4-heptadienoic acid (**10**)

[0120] Following a procedure analogous to that described in Example 1, step 3, but substituting diene ester **9** for **3** the title compound was obtained in 79% yield: ^{1}H NMR (300 MHz, CD_3OD) δ 7.29 (m, 5H), 7.18 (dd, J = 15.3,10.5 Hz, 1H), 6.16 (m, 2H), 5.75 (d, J = 15.3 Hz, 1H), 4.22 (br t, J =6.6 Hz, 1H), 3.19 (s, 3H), 2.61 (m, 1H), 2.48 (m,1H).

Step 4: 7-Methoxy-7-phenyl-2,4-heptadienoic acid chloride (**11**)

[0121] Following a procedure analogous to that described in Example 1, step **4**, but substituting carboxylic acid **10** for **4**, the title compound was obtained in a quantitative yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.45 (m, 6H), 6.30 (m, 2H), 6.10 (d, J = 15.0 Hz, 1H), 4.23 (dd, J = 7.5,5.4 Hz, 1H), 3.22 (s, 3H), 2.63 (m, 1H), 2.49 (m, 1H).

Step 5: *N*-Hydroxy-7-methoxy-7-phenyl-2,4-heptadienamide (**12**)

[0122] Following a procedure analogous to that described in Example 1 step 5 but substituting acid chloride **11** for **5** the title compound was obtained in 45% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 7.15 (dd, J =14.7,10.5 Hz, 1H), 6.05 (m, 2H), 5.73 (d, J= 14.7 Hz, 1H), 4.17 (dd, J = 8.4,4.8 Hz, 1H), 3.19 (s, 3H), 2.61 (m, 1H), 2.43 (m,1H); ^{13}C NMR (75.4 MHz, $CDCl_3$)
δ 41.6, 56.6, 83.1, 118.0, 126.5, 127.8, 128.4, 130.4, 139.0, 140.1, 141.6, 165.5.

Example 3:

***N*-Hydroxy-7-methoxy-7-[4-(*N*,*N*-dimethylamino)phenyl]-2,4-heptadienamide (17)**

Step 1: 5-Methoxy-5-[4-(*N*,*N*-dimethyamino)phenyl]-2-pentanal (**14**)

[0123] Following a procedure analogous to that described in Example 1, step 1, but substituting 4-dimethylaminobenzaldehyde dimethyl acetal (**13**) for *p*-anisaldehyde dimethyl acetal (**1**), the title compound **14** was obtained in 39% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, J = 8.1 Hz, 1H), 7.16 (d, J = 8.7 Hz, 2H), 6.83 (dt, J = 15.6,6.9 Hz, 1H), 6.71 (d, J = 8.7 Hz, 2H), 6.12 (ddt, J =15.6, 7.8, 1.5 Hz, 1H), 4.23 (dd, J = 8.1, 5.1 Hz, 1H), 3.19 (s, 3H), 2.96 (s, 6H), 2.81 (m, 1H), 2.65 (m, 1H).

Step 2: Ethyl 7-methoxy-7-[4-(*N*,*N*-dimethylamino)phenyl]-2,4-heptadienoate (**15**)

[0124] Following a procedure analogous to that described in Example 1, step 2, but substituting aldehyde **14** for **2**, the title compound **15** was obtained in 87 % yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (dd, J = 15.3, 10.2 Hz, 1H), 7.13 (d, J = 9.0 Hz, 2H), 6.71 (d, J = 9.0 Hz, 2H), 6.01-6.23 (m, 2H), 5.76 (d, J = 15.3 Hz, 1H), 4.18 (q, J =7.2 Hz, 2H), 4.13 (dd, J = 7.8,6.0 Hz, 1H), 3.18 (s, 3 H), 2.96 (s, 3H), 2.66 (m, 1H), 2.50 (m, 1H), 1.28 (t, J = 7.2Hz, 3H).

Step 3: 7-Methoxy-7-[4-(*N*,*N*-dimethylamino)phenyl]-2,4-heptadienoic acid (**16**)

[0125] Following a procedure analogous to that described in Example 1, step **3**, but substituting diene ester **15** for **3**, the title compound **16** was obtained in 97% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, J = 15.3,10.2 Hz, 1H), 7.15 (d, J = 9.0 Hz, 2H), 6.73 (d, J = 9.0 Hz, 2H), 6.17 (m, 2H), 5.77 (d, J =15.3Hz,1H), 4.20 (m, 1H), 3.19 (s, 3 H), 2.96 (s, 6H), 2.68 (m, 1H), 2.52 (m, 1H).

Method B

Step 4: *N*-Hydroxy-7-methoxy-[4-(*N*,*N*-dimethylamino)phenyl]-2,4-heptadienamide (**17**)

[0126] To a solution of carboxylic acid **16** (110 mg, 0.40 mmol) in anhydrous THF (5 mL) was added 1,1'-carbonyldiimidazole (77 mg, 0.439 mmol) at rt, and the mixture was stirred overnight. To this solution was added *t*-butyldimethylsilylhydroxylamine (200 mg, 1.36 mmol). The mixture was stirred at rt for 14 h and then at 45 ˚C for 3 h. The resulting yellow solution was diluted with water (5 mL), stirred for 20 minutes, and then extracted with ethyl acetate (3 × 15 mL),

dried, and concentrated. Purification by flash silica gel chromatography (80% ethyl acetate in hexanes and then ethyl acetate only) afforded the title compound 17 (44 mg, 38% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, J = 15.0,10.2 Hz, 1H), 7.13 (d,J=8.7Hz,1H),6.71 (d, J = 8.7 Hz, 2H), 5.96-6.17 (m, 2H), 5.66 (br d, J = 15.0 Hz, 1H), 4.09 (dd, j = 7.5,5.7 Hz, 1H), 3.17(s, 3H), 2.94 (s, 6H), 2.61 (m, 1H),2.43 (m,1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 40.6, 41.5, 56.2, 82.9, 112.4, 117.4, 127.6, 128.7, 130.1, 139.9, 141.9, 150.3, 165.5.

Example 4:

***N*-(2-Aminophenyl)-7 methoxy-7-(4-methoxyphenyl)-2,4-heptadienamide (18)**

[0127] To a stirred solution of acid chloride **5** (115 mg,0.41 mmol) in CH_2Cl_2 (5 mL) at 0 ˚C was added 1,2-phenylenediamine (133 mg,1.23 mmol) followed by *N*-methylmorpholine (49 μL, 0.45 mmol). The mixture was stirred at 0 ˚C for 1 h, and then was allowed to warm to rt over 1 h. After being stirred for an additional 1 h at rt, the reaction mixture was partitioned between $CHCl_3$ (2 × 15mL) and water (15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Purification by flash silica gel chromatography (50% ethyl acetate in hexane) afforded the desired benzamide **18** (21 mg, 15% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65-7.40 (m, 9H), 5.96-6.20 (m, 2H), 5.92 (d, J = 15.3 Hz, 1H), 4.18 (m,1H), 3.82 (br s, 2H), 3.81 (s, 3H), 3.19 (s, 3H), 2.61 (m, 1H), 2.43 (m,1H); ^{13}CNMR (75.4 MHz,$CDCl_3$) δ 41.7, 55.2, 56.4, 82.7, 113.8, 118.2, 119.5, 121.8, 124.4, 125.0, 127.0, 127.8, 130.1, 133.1, 139.5, 140.7, 142.4, 159.2, 164.6.

Example 5:

***N*-(2-Aminophenyl)-7-methoxy-7-phenyl-2,4-heptadienamide (19)**

Step 1: *N*-[2-(*N*-*tert*-Butoxycarbonyl)aminophenyl]-7-methoxy-7-phenyl-2,4-heptadienamide

[0128] Following a procedure analogous to that described in Example 4, but substituting acid chloride **11** for **5** and *t*-Boc protected phenylenemonoamine for 1,2-phenylenediamine, the title compound was obtained as a light yellow solid in 84% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.01-7.49 (m, 10H), 6.09 (m, 2H), 5.87 (d, J =15.3 Hz, 1H), 4.21 (dd, J = 7.5,5.7 Hz,1H), 3.23 (s, 3H), 2.66 (m, 1H), 2.52 (m, 1H), 1.51 (s, 9H).

Step 2: *N*-(2-Aminophenyl)-7-methoxy-7-phenyl-2,4-heptadienamide (**19**)

[0129] The *t*-Boc protected aniline obtained in step 1 (200 mg, 0.473 mmol) was dissolved in a mixture of methanol (2 mL) and 4*N* HCl solution in 1,4-dioxane (3.55 mL, 14.2 mmol) and stirred at rt for 1 h. The reaction mixture was diluted with water (2 mL), neutralized with 1N NaOH (pH 7-8), and extracted with $CHCl_3$. The organic extract was dried($MgSO_4$) and concentrated: Purification by flash silica gel chromatography (50% ethyl acetate in hexane) afforded the title compound **19** (128 mg, 84% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (br s, 1H), 7.01- 7.39 (m, 10H), 6.09 (m, 2H), 5.91 (d, J =14.7 Hz, 1H), 4.20 (br. t, J = 6.3 Hz, 1H), 3.81 (br. s, 2H), 3.21 (s, 3H), 2.66 (m,1H), 2.52 (m,1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 41.7, 56.7, 83.2, 118.1, 119.4, 121.9, 124.4, 125.1, 126.6, 127.1, 127.8, 128.5, 130.3, 139.2, 140.8, 141.2, 142.3, 164.6.

Example 6:

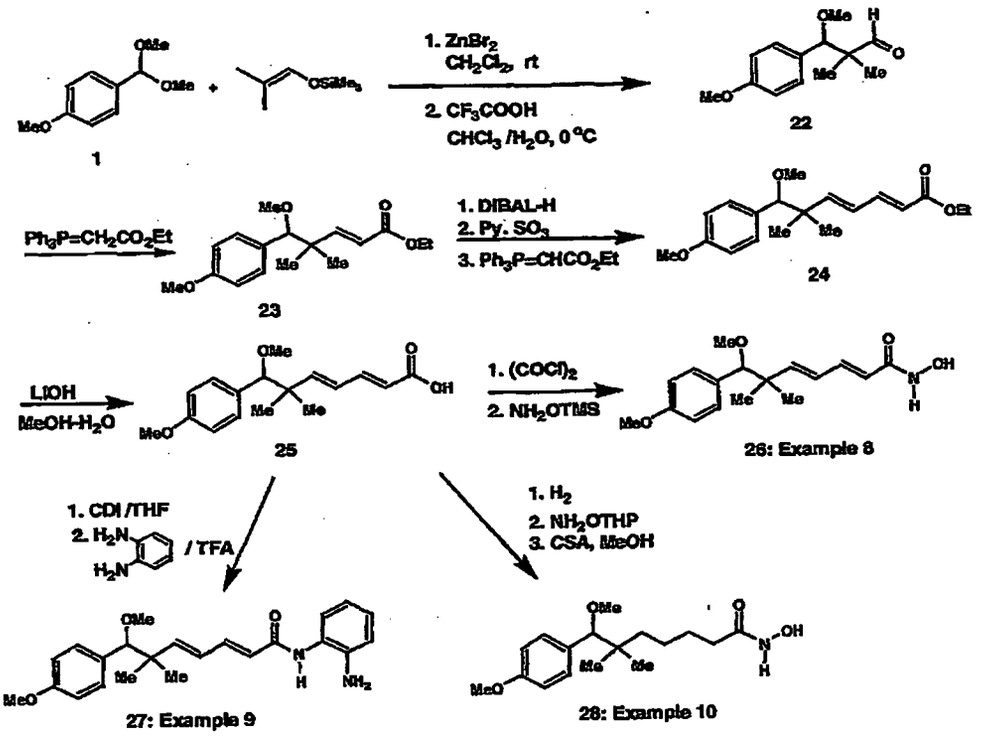
***N*-(2-Aminophenyl)-7-methoxy-7-[4-(*N,N*-dimethylamino)phenyl]-2,4-heptadienamide (20)**

[0130] To a solution of carboxylic acid **16** (207 mg, 0.753 mmol) in anhydrous THF (10 mL) was added 1,1'-carbonyldiimidazole (128 mg, 0.790 mmol) at rt, and the mixture was stirred overnight. To the resulting solution was added 1,2-phenylenediamine (570 mg, 5.27 mmol), followed by trifluoroacetic acid (52 μl), and the reaction mixture was stirred for 16 h at rt. The reaction mixture was diluted with ethyl acetate (30 mL), washed with saturated $NaHCO_3$ solution (5 mL) and then water (10 mL), dried ($MgSO_4$), and concentrated. Purification by flash silica gel chromatography (50% ethyl acetate in toluene) afforded the title compound **20** (115 mg, 42% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (br.s, 1H), 7.01-7.29 (m, 5H), 6.70-6.78 (m, 4H), 6.09 (m, 2H), 5.90 (d, J =15.0 Hz,1H), 4.10 (br. t, J = 6.6 Hz,1H), 3.89 (br . s, 2H), 3.18 (s, 3H), 2.95 (s, 3H), 2.66 (m,1H), 2.50 (m,1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 40.5, 41.6, 82.8, 112.3, 118.1, 119.4, 121.7, 124.4, 125.1, 127.0, 127.6, 128.6, 130.0, 140.0, 140.8, 142.5, 150.2, 164.7.

Example 7:

***N*-(2-Aminopyridinyl)-7-methoxy-7-(4-methoxyphenyl)-2,4-heptadienamide (21)**

[0131] Following a procedure analogous to that described in Example 1, step 5, but substituting 2-aminopyridine for trimethylsilyloxyhydroxylamine, the title compound was obtained in 5% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31-8.23 (m, 3H), 7.70 (m, 1H), 7.31 (dd, J = 15.0,10.5 Hz, 1H), 7.19 (d, J = 9.0 Hz, 2H), 7.02 (m, 1H), 6.89 (d, J = 9.0 Hz, 2H), 6.13 (m, 2H), 5.90 (d, J = 15.0 Hz, 1H), 4.16 (dd, J = 7.2, 6.0 Hz, 1H), 3.82 (s, 3H), 3.20 (s, 3H), 262 (m, 1H), 247 (m,1H).



[0132] Examples 8 and 9 are for illustration purpose only.

Example 8:

***N*-Hydroxy-6,6-dimethyl-7-methoxy-7-(4-methoxyphenyl)-2,4-heptadienamide (26)**

Step1: 2,2-Dimethyl-3-methoxy-3(4-methoxyphenyl)propanal (**22**)

[0133] Following a procedure analogous to that described in Example 1, step 1, but substituting 2-methyl-1-(trimethylsilyloxy)-1-propene for 1-trimethylsilyloxy-1,3-butadiene, the title compound **22** was obtained in 65% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.17 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz), 4.26 (s, 1H), 3.82(s, 3H), 3.17 (s, 3H), 1.00 (s, 3H), 0.89 (s, 3H).

Step 2: Ethyl 4,4-dimethyl-5-methoxy-5-(4-methoxyphenyl)-2-pentenoate (**23**)

[0134] Following a procedure analogous to that described in Example 1, step 2, but substituting aldehyde **22** for aldehyde **2** and conducting the reaction in refluxing toluene, the title compound **23** was obtained in 93% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J =15.9 Hz, 1H), 7.26 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 5.83 (d, J = 15.9 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 4.04 (s, 1H), 3.9 7 (s, 3H), 3.32 (s, 3H), 1.45 (t, J =7.2 Hz, 3H), 1.20 (s, 3H), 1.14 (s, 3H).

Step 3: Ethyl 6,6-dimethyl-7 methoxy-7-(4-methoxphenyl)-2,4-heptadienoate (**24**)

i) DIBAL-H Reduction

[0135] To a stirred solution of ester **23** (2.14g, 7.32 mmol) in anhydrous THF (40mL) was added dropwise a solution of DIBAL-H (1.0*M* solution in THF, 16 mL,16 mmol) via syringe at -78˚C, and the mixture was slowly warmed to rt over 3 h with stirring. The reaction was quenched carefully with water (20 mL), extracted with ethyl acetate (30 × 3 mL), dried ($MgSO_4$), and concentrated. Purification by flash silica gel chromatography (25% ethyl acetate in hexane) afforded the corresponding alcohol (1.46 g, 80% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.80 (dt, J = 15.9,1.4 Hz, 1H), 5.48 (dt, J =15.9,6.0 Hz, 1H), 4.10 (d, J = 6.0 Hz, 2H), 3.82 (s, 1H), 3.81 (s, 3H), 3.16 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H), 1.00 (s, 3H), 0.95 (s, 3H).

ii) Oxidation

[0136] To a stirred solution of the alcohol (1.21 g, 4.84 mmol) in anhydrous DMSO (25 mL) containing triethylamine (4.3 mL) was added pyridinium sulfur trioxide complex (2.31 g, 14.5 mmol) at rt, and the mixture was stirred for 10 min. at the same temperature. The reaction was quenched by adding cold water (15 mL). Extraction with ethyl ether (3 × 30 mL), followed by drying and concentration gave the corresponding aldehyde, which was used without further purification in the next step.(1.03 g, 86% yield).

iii: Wittig Reaction

[0137] The aldehyde was treated with ethyl (triphenylphosphoranylidene)acetate in toluene at 70 ˚C by a procedure analogous to that described in Example 1, step 2, to give the title compound **24** in 93% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, J = 15.3, 10.5 Hz, 1m, 7.10 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.25 (d, J = 15.6 Hz, 1H), 6.01 (dd, J = 15.6,10.5 Hz, 1H), 5.76 (d, J = 15.3 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.83 (s, 1H), 3.81 (s, 3H), 3.15 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.06 (s, 3H), 0.96 (s, 3H).

Step 4: 6,6-Dimethyl-7-methoxy-7-(4-methoxyphenyl)-2,4-heptadienoic acid (**25**)

[0138] Following the procedure described in Example 1, step 3, but substituting compound **24** for diene ester 3, the title compound **25** was obtained in 95% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, J =15.0,10.8. Hz,1H), 7.10 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0 Hz, 2H), 6.32 (d, J =15.6Hz, 1H), 6.06 (dd, J = 15.6, 10.8 Hz, 1H), 5.78 (d, J =15.3 Hz,1H), 3.85 (s,1H), 3.81 (s, 3H), 3.16 (s, 3H), 1.08 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 22.9, 24.4, 42.2, 55.1, 57.2, 90.6,113.9,118.7, 125.7,129.4,130.3,147.9,152.4,159.0,172.8.

Step 5: *N*-Hydroxy-6,6-dimethyl-7-methoxy-7-(4-methoxyphenyl)-2,4-heptadienamide (**26**)

[0139] Following the procedure described in Example 1, step 4 (Method A), but substituting compound **25** for carboxylic acid **4**, the title compound **26** was obtained as a colorless solid in 63% overall yield: ^{1}H NMR (300 MHz, CD_3OD) δ 7.21 (dd, J = 15.3,10.8 Hz, 1H), 7.15 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.25 (d, J =15.6 Hz, 1H), 6.03 (dd, J = 15.6,10.8 Hz, 1H), 5.83 (d, J = 15.3 Hz, 1H), 3.93 (s, 1H), 3.80 (s, 3H), 3.17 (s, 3H), 1.09 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 23.7, 24.9, 43.0, 55.6, 57.4, 91.9, 114.0, 119.7, 127.1, 130.6, 131.7, 142.6, 150.7,160.6,166.8.

Example 9:

***N*-(2-Aminophenyl)-6,6-dimethyl-7-methoxy-7-(4-methoxyphenyl)-2,4-heptadienamide (27)**

[0140] Following the procedure described in Example 6, but substituting carboxylic acid **25** for carboxylic acid **16**, the title compound **27** was obtained as a light yellow solid in 67% yield: ^{1}H NMR (300 MHz, CD_3OD) δ 7.56 (br. s, 1H), 7.29 (dd, J =15.0,10.8 Hz,1H), 6.72- 7.20 (m, 8H), 6.20 (d, J =15.0 Hz,1H), 5.98 (dd, J =15.0,10.8 Hz, 1H), 5.90 (d, J = 15.0 Hz, 1H), 3.91 (br s, 2H), 3.83 (s, 1H), 3.80 (s, 3H), 3.16(s, 3H), 1.06 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 23.2, 24.3, 42.1, 55.1, 57.2, 90.6, 112.9, 118.0, 119.4, 121.6, 124.4, 125.2, 125.6, 127.0, 129.4, 130.5,140.8,143.1,150.3,158.9,164.9.

Example 10:

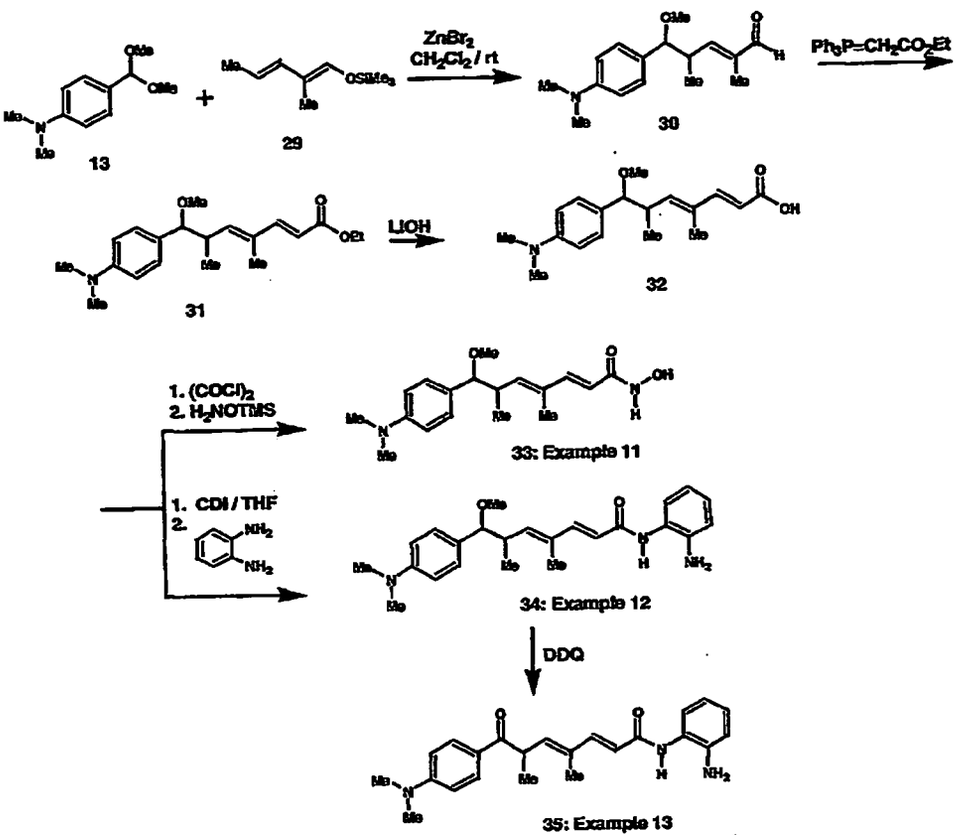
***N*-Hydroxy-6,6-dimethyl-7-methoxy-7-(4-methoxyphenyl)heptanamide (28)**

Step 1: 6,6-Dimethyl-7-methoxy-7-(4-methoxyphenyl)heptanoic acid

[0141] To a solution of carboxylic acid **25** (100 mg, 0.345 mmol) in MeOH (6 mL), at room temperature was added a solution of Pd/C 10% (50 mg, 1 mL in MeOH). The system was then purged with H_2 several times to a final pressure of 50 psi. The reaction mixture was stirred for 3 h at room temperature, and then the solid was filtered through a Celite pad in a fritted glass funnel. The solvents were evaporated, and the crude material (100 mg, 99%) was pure enough for use in the next step: ^{1}H NMR (300 MHz d_6-acetone) δ 7.18 (d, J = 8 Hz, 2H), 6.89 (d, J = 8 Hz, 2H), 3.85 (s, 1H), 3.78 (s, 3H), 3.11 (s, 3H), 2.30 (br. t, J = 7.5 Hz, 2H), 1.58-1.53 (m, 2H), 1.37-1.25 (m, 4H), 0.84 (s, 3H), 0.77 (s, 3H).

Step 2: *N*-Hydroxy-6,6-dimethyl-7-methoxy-7-(4-methoxyphenyl)heptanamide **(28)**

[0142] To a solution of the carboxylic acid from step 1 (100 mg, 0.344 mmol), in DMF (10 mL) at room temperature were added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC, 79 mg, 0.414 mmol) and 1-hydroxy-benzotriazole hydrate (HOBt, 70 mg, 0.516 mmol). The mixture was stirred for 20 min. at room temperature, and then NH_2OTHP (60 mg, 0.516 mmol) was added. The resulting mixture was heated overnight at 50˚C, and then concentrated. The crude material was dissolved in CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted several times with CH_2Cl_2 and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated. The crude material was purified by flash chromatography using hexane/acetone (7:3) as the solvent mixture. The pure protected hydroxamate was then dissolved in MeOH (10 mL), and 10-camphorsulfonic acid (CSA, 40 mg, 0.172 mmol) was added. The mixture was stirred for 2 h at room temperature, and then the solvents were evaporated under reduced pressure at room temperature to avoid thermal decomposition. The crude mixture was purified by flash chromatography using CH_2Cl_2/MeOH (9:1) as the solvent mixture, giving compound **28** as colorless oil (212 mg, 68%): ^{1}H NMR: (300 MHz, d_6-acetone) δ = 7.18 (d, J = 8Hz, 2H), 6.89 (d, J = 8Hz, 2H), 3.85 (s, 1H), 3.79 (s, 3H), 3.11 (s, 3H), 2.11-2.05 (m, 2H), 1.45 (br. s, 2H), 1.34 (br. s, 4H), 0.83 (s, 3H), 0.76 (s, 3H).



[0143] Examples 11-13 are for illustration purpose only.

Example 11:

***N*-Hydroxy-4,6-dimethyl-7-methoxy-7-[4-(*N*,*N*-dimethylamino)phenyl]-2,4-heptadienamide (33)**

Step 1: 2,4-Dimethyl-5-methoxy-5-[4-(*N*-dimethylamino)phenyl]-2-pentenal (30)

[0144] Following the procedure described in Example 1, step 1, but substituting 2-methyl-1-trimethylsilyloxypenta-1,3-diene (**29**) (Tetrahedron, 39: 881 (1983)) for 1-trimethylsilyloxy-1,3-butadiene, the title compound **30** was obtained in 68% yield as a mixture of two isomers in a ca. 2.5:1 ratio: **major isomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.67 (d, J =8.4 Hz, 2H), 6.29 (dq, J = 9.9, 1.2 Hz, 1H), 3.96 (d, J = 6.6 Hz, 1H), 3.20 (s, 3H), 3.05 (m, 1H), 2.94 (s, 6H), 1.60 (d, J = 0.9 Hz, 3H), 1.12 (d, J = 6.9 Hz, 3H).

Step 2: Ethyl 4,6-dimethyl-7-methoxy-7-[4-(*N*,*N*-dimethylamino)phenyl]-2,4-heptadienoate (31)

[0145] Following the procedure described in Example 1, step **2**, but substituting aldehyde **30** for aldehyde **2** and heating the reaction mixture at reflux in toluene overnight under N_2, the title compound **31** was obtained in 96 % yield as a mixture of two isomers in a ca. 2.5 : 1 ratio: **major isomer**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (dd, J = 15.6, 0.9 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 6.66 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 15.6Hz, 1H), 5.67 (br. d, J = 9.0 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.87 (d, J = 6.9Hz, 1H), 3.18 (s, 3H), 2.93 (s, 6H), 2.81 (m, 1H), 1.59 (d, J = 1.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.05 (d, 6.6 Hz, 3H).

Step 3: 4,6-Dimethyl-7-methoxy-7-(4-*N*,*N*-imethylaminophenyl)-2,4-heptadienoic acid (32)

[0146] Following the procedure described in Example 1, step 3, but substituting ester **31** for ester **3**, the title compound **32** was obtained in 98 % yield: **major isomer**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.21 (d, J = 15.6, 0.6 Hz, 1H), 7.04 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 8.7 Hz, 2H), 5.61 (d, J = 15.6 Hz, 1H), 5.60 (br. d, J =10.0 Hz, 1H), 3.85 (d, J = 7.5 Hz, 1H), 3.13 (s, 3H), 2.87 (s, 6H), 2.81 (m, 1H), 1.52 (d, J = 1.5 Hz, 3H), 1.06 (d, J = 6.6 Hz, 3H).

Step 4: *N*-Hydroxy-4,6-dimethyl-7-methoxy-7-[4-(*N*,*N*-dimethylamino)phenyl]-2,4-heptadienamide (**33**)

[0147] Following the procedure described in Example 1, step **4** (Method A), but substituting compound **32** for carboxylic acid **4**, the title compound **33** was obtained in 5 % yield, as a mixture of two isomers in a ca. 3 : 1 ratio: major isomer. ^{1}H NMR (300 MHz, CD_3OD) δ 7.23-7.21 (m, 3H), 6.67 (d, J = 8.7 Hz, 2H), 5.70 (d, J = 15.6 Hz, 1H), 5.62 (d, J = 10.2 Hz, 1H), 3.90 (d, J = 7.8 Hz, 1H), 3.20 s, 3H), 2.93 (s, 6H), 2.81 (m, 1H),1.58 (br. s, 3H), 1.13 (d, J = 6.6 Hz, 3H).

Example 12:

***N*-(2-Aminophenyl)-4,6-dimethyl-7-methoxy-7-[4-(*N*,*N*-dimethylamino)phenyl]-2,4-heptadienamide (34)**

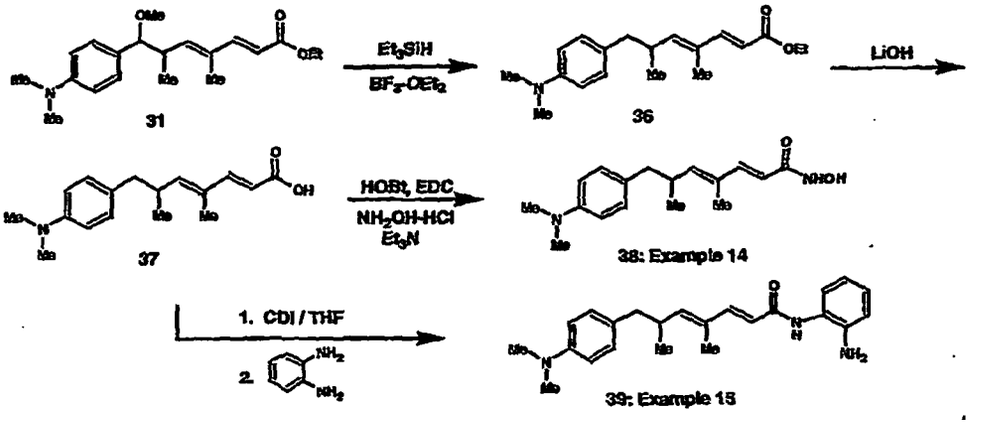
[0148] Following the procedure described in Example 6, but substituting carboxylic acid **32** for carboxylic acid **16**, the title compound **34** was obtained in 61% yield, as a mixture of two isomers in a ca.3 : 1 ratio: **major isomer**. ^{1}H NMR (300 MHz, CD_3OD) δ 7.28-7.02 (m, 5H), 6.79 (m, 2H), 6.68 (d, J = 8.7 Hz, 2H), 5.83 (d, J = 15.0 Hz, 1H), 5.69 (d, J = 9.6 Hz, 1H), 3.87 (d, J = 6.9 Hz, 1H), 3.19 (s, 3H), 2.94 (s, 6H), 2.80 (m, 1H),1.61 (br. s, 3H), 1.07 (d, J = 6.6 Hz, 3H).

Example 13 :

***N*-(2-Aminophenyl)-4-methyl-6-[4-(*N*,*N*-dimethylamino)benzoyl]-2,4-heptadienamide (35)**

[0149] To a stirred solution of compound **34** (85 mg, 0.216 mmol) in wet benzene (2 mL, benzene : H_2O = 9 : 1) at room temperature was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 98 mg, 0.432 mmol). After being stirred vigorously for 15 min., the mixture was diluted with ethyl acetate (30 mL), washed with water (2 × 5 mL), dried (anhydr.$MgSO_4$), and concentrated. Purification by flash silica gel chromatography (50% ethyl acetate in hexanes, and then ethyl acetate only) afforded the title compound **35** (6 mg, 7% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 9.0, 2H), 7.87 (br. s, 1H), 7.29 (d, J = 15.6 Hz, 1H), 7.27 (d, 7.8 Hz, 1H), 7.00 (m, 1H), 6.72 (m, 2H), 6.62 (d, J = 9.0 Hz, 2H), 5.97 (d, J = 15.6 Hz, 1H), 5.97 (d, J = 9.3Hz, 1H), 4.34 (dq, J = 9.3, 6.9 Hz, 1H), 3.03 (s, 3H), 1.87 (br. s, 3H), 1.29 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 17.6, 39.9, 40.8, 110.7, 118.0, 119.0, 119.3, 123.8, 124.4, 125.1, 126.9,

130.6, 132.5, 140.8, 146.2, 153.4, 164.8, 198.6.



[0150] Examples 14 and 15 are for illustration purpose only.

Example 14:

N-Hydroxy-4,6-dimethyl-7-[4-(*N*,*N*-dimethylamino)phenyl]-2,4-heptadienamide (38)

Step 1: Ethyl 4,6-dimethyl-7-[4-(*N*,*N*-dimethylamino)phenyl]-2,4-heptadienoate (**36**)

[0151] To a stirred solution of ester compound **31** (99 mg, 0.299 mmol) in CH_2Cl_2 (3 mL) at 0 ˚C was added triethylsilane (41.9 mg, 0.36 mmol) followed by BF_3 Et_2O (51 mg, 0.36 mmol) dropwise via microsyringe, and the mixture was stirred at 0 ˚C for 30 min. The reaction was quenched with saturated $NaHCO_3$ solution (3 mL), diluted with CH_2Cl_2 (20 mL), and washed with water, and the organic phase was dried and concentrated. Purification by flash silica gel chromatography (10% ethyl acetate in hexane) afforded the title compound **36** (87 mg, 97% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dd, J = 15.6, 0.6 Hz, 1H), 6.98 (d, J = 8.7 Hz, 2H), 6.64 (d, J = 8.7 Hz, 2H), 5.74 (d, J =15.6 Hz, 1H), 5.73 (br d, J =10.2 Hz, 1H), 4.20 (q, J = 6.9 Hz, 2H), 2.90 (s, 6H), 2.73 (m, 1H), 2.53 (d, J = 7.2 Hz, 2H), 1.61 (d, J = 0.6 Hz, 3H), 1.29 (t, J = 6.9 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 14.3, 20.0, 35.5, 40.8, 42.2, 60.1, 112.7, 115.5, 128.1, 129.1, 131.6, 147.5, 149.0, 149.8, 167.5.

Step 2: 4,6-Dimethyl-7-[4-(*N*,*N*-dimethylamino)phenyl]-2,4-heptadienoic acid (37)

[0152] Following the procedure described in Example 1, step 3, but substituting compound **36** for ester **3**, the title compound **37** was obtained in 98 % yield as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, J = 15.6, 0.6 Hz, 1H), 6.98 (d, J = 9.0 Hz, 2H), 6.67 (d, J = 9.0 Hz, 2H), 5.79 (br. d, J = 9.6 Hz, 1H), 5.73 (d, J = 15.6 Hz, 1H), 2.91 (s, 6H), 2.76 (m, 1H), 2.57 (d, J = 7.2 Hz, 2H), 1.62 (d, J = 0.6 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$)
δ 12.2, 20.0, 35.7, 40.9, 42.17, 112.9, 114.7, 128.2,
129.7, 131.7, 148.9, 149.1, 152.1, 172.7.

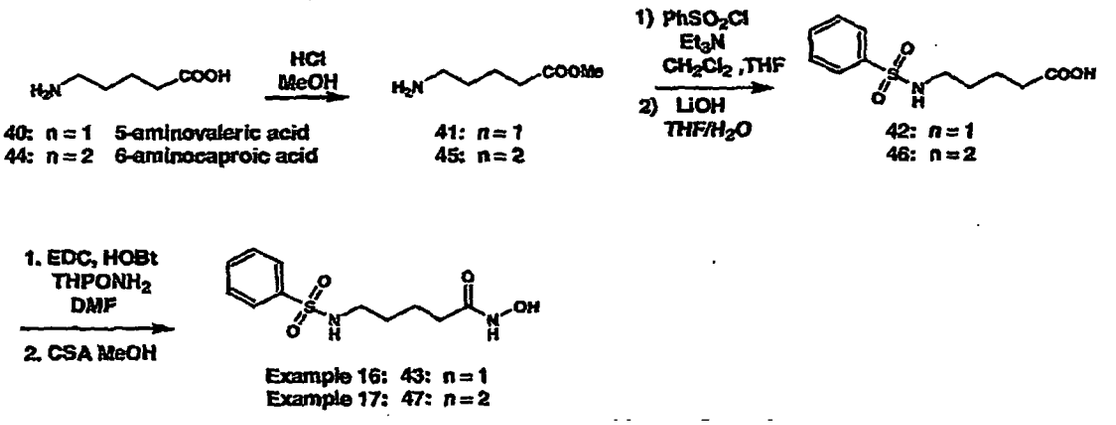
Step 3: *N*-Hydroxy-4,6-dimethyl-7-[4-(*N*,*N*-dimethylamino)phenyl]-2,4-heptadienamide (**38**)

[0153] To a stirred solution of carboxylic acid **37** (70 mg, 0.256 mmol) at rt in anhydrous DMF (2 mL) was added 1-hydroxybenzotriazole hydrate (41.5 mg, 0.307 mmol) followed by 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride(65 mg, 0.340 mmol). After 1 h, hydroxylamine hydrochloride (89 mg, 1.28 mmol) and Et_3N (0.27 mL, 1.92 mmol) was added, and stirring was continued at rt overnight. The solvent was removed in vacuo, and the residue was diluted with ethyl acetate (30 mL), and washed with water and saturated $NaHCO_3$ solution (5 mL). After drying and concentration, the crude product was purified by flash silica gel chromatography (2-10% methanol in chloroform) to give the title compound **38** (30 mg, 41% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$: CD_3OD = 5:1) δ 7.10 (d, J = 14.4 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 6.58 (d, J = 8.7 Hz, 2H), 5.59 (d, J = 9.3Hz, 1H), 5.55 (br. d, J = 14.4 Hz, 1H), 2.78 (s, 6H), 2.63 (m, 1H) 2.40 (d, J = 6.9 Hz, 2H), 1.48 (s, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$: CD_3OD = 5:1)
δ 11.8, 19.7, 35.3, 40.8, 42.0, 14.3, 20.0, 35.5, 40.8, 42.2, 113.1, 113.7, 128.7, 129.5, 131. 1, 145.9, 146.3, 148.9, 165.5.

Example 15:

***N*-(2-Aminophenyl)-7-[4-(*N*,*N*-dimethylamino)phenyl)]-4,6-methyl-2,4-heptadienamide (39)**

[0154] Following the procedure described in Example 6, but substituting carboxylic acid **37** for carboxylic acid **16**, the title compound **39** was obtained in 75% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (br. s, 1H), 7.32 (d, J = 15.0 Hz, 1H), 7.20 (d, J = 7.2Hz, 1H), 7.04 (t, J = 7.2Hz, 1H), 6.98 (d, J = 9.0 Hz, 2H), 6.76 (m, 2H), 6.66 (d, J = 9.0 Hz, 2H), 5.85 (d, J = 15.0 Hz, 1H), 5.72 (d, J = 9.6 Hz, 1H), 3.90 (br. s, 2H), 2.90 (s, 6H), 2.75 (m, 1H), 2.52 (d, J = 7.2 Hz, 2H), 1.61 (d, J = 0.6 Hz, 3H). 1.00 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 20.1, 35.6, 40.9, 42.2, 112.7, 111.5, 118.1, 119.4, 124.6, 125.1, 126.9, 128.2,129.7, 131.3, 140.8, 147.1, 47.4, 149.0, 165.0.



[0155] Examples 16 and 17 are for illustration purpose only.

Example 16:

***N*-Hydxoxy-5-(benzenesulfonylamino)pentanamide (43)**

Step 1: Methyl 5-aminovalerate (**41**)

[0156] To a solution of 5-aminovaleric acid (5 g, 42.68 mmol) in MeOH (100 mL) at room temperature was added HCl conc. (37%, 16 mL). The solution was stirred for 48 h at room temperature and monitored by HPLC-MS. The resulting solution was treated with a saturated aqueous solution of $NaHCO_3$ then the solvents were evaporated under reduced pressure. The aqueous layer was washed several times with CH_2Cl_2 and AcOEt. The aqueous phase was concentrated to produce a solid containing the desired product, NaCl, and $NaHCO_3$. The solid was washed with MeOH, and the organic filtrate was concentrated to afford the title compound (**36**) as a white solid (7.88 g, 100%): ^{1}H NMR: (300 MHz, CD_3OD) δ 3.34 (s, 3H), 2.61 (br. s, 2H), 2.10-2.06 (m,2H), 1.39-1.34 (m, 4H); MS (ES) m/z 132.2 (M^+).

Step 2: 5-(Benzenesulfonylamino)pentanoic acid (**42**)

[0157] To a solution of **41** (3 g, 22.90 mmol), in a solvent mixture of CH_2Cl_2 (100 mL) and THF (50 mL) at room temperature were added Et_3N (7.96 mL, 57.25 mmol), followed by benzenesulfonyl chloride (6.13 mL, 48.09 mmol). The mixture was stirred overnight at room temperature and then treated with a saturated aqueous solution of NH_4Cl. The phases were separated and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic extracts were dried over ($MgSO_4$) and evaporated under reduced pressure giving a mixture of mono- and bis-alkylated products. The residue was dissolved in THF (50 mL) and water (50 mL), and LiOH was added. The resulting mixture was stirred for 4 h at room temperature, and then was treated with 1N HCl until pH 1. The phases were separated and the aqueous layer was extracted several times with AcOEt. The combined organic extracts were dried over ($MgSO_4$) and then evaporated under reduced pressure, yielding compound 42 (2.95 g, 48%) as a white powder. ^{1}H NMR (300 MHz, acetone-d_6) δ 7.86 (d, J = 7 Hz, 2H), 7.64-7.57 (m, 3H), 6.47 (br. s, 1H), 2.96-2.89 (m, 2H), 2.27-2.23 (m, 2H), 1.60-1.50 (m, 4H).

Step 3: *N*-Hydroxy-5-(benzenesulfonylamino)pentanamide (**43**)

[0158] To a solution of **42** (500 mg, 1.95 mmol) in DMF (20 mL) at room temperature were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 448 mg, 2.33 mmol), and 1-hydroxybenzotriazole hydrate (HOBT, 395 mg, 2.93 mmol). The mixture was stirred 20 min. at room temperature, and then $THPONH_2$ (342 mg, 2.93 mmol) was added. The resulting mixture was heated at 50˚C for 24 h, and then the DMF solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 and washed with brine and a saturated aqueous solution of $NaHCO_3$. The combined organic extracts were dried over ($MgSO_4$) and then evaporated. The crude compound was purified by flash chromatography using hexane-acetone (1:1) as the solvent mixture. The residue was then dissolved in MeOH (10 mL), and 10-camphorsulfonic acid (CSA, 226 mg, 975 mmol) was added. The mixture was stirred for 2 h at room temperature, and then the solvents were evaporated under reduced pressure at room temperature to avoid thermal decomposition. The crude product was purified by flash chromatography using CH_2Cl_2/MeOH(9:1) as solvent mixture giving compound **43** as a yellowish oil (259 mg, 48% isolated): ^{1}H NMR (300 MHz, acetone-d_6) δ 9.99 (br. s, 1H), 7.87 (br. s, 2H), 7.62 (br. s), 2.90 (br. s, 2H), 2.05 (br. s, 2H), 1.59-1.49 (m, 4H).

Example 17:

***N*-Hydroxy-6-(benzenesulfonylamino)hexanamide (47)**

Step 1: Methyl 6-aminocaproate (**45**)

[0159] Compound **45** was prepared in 100% yield, using the procedure described in Example 16, step 1, but substituting 6-aminocaproic acid for 5-aminovaleric acid. ^{1}H NMR (300 MHz, CD_3OD) δ 3.33 (s, 3H), 2.56-2.51 (m, 2H), 2.06-2.01 (m, 2H, 1.35-1.28 (m, 4H), 1.10-1.00 (m, 2H); MS (ES) m/z 146.2 (M^+).

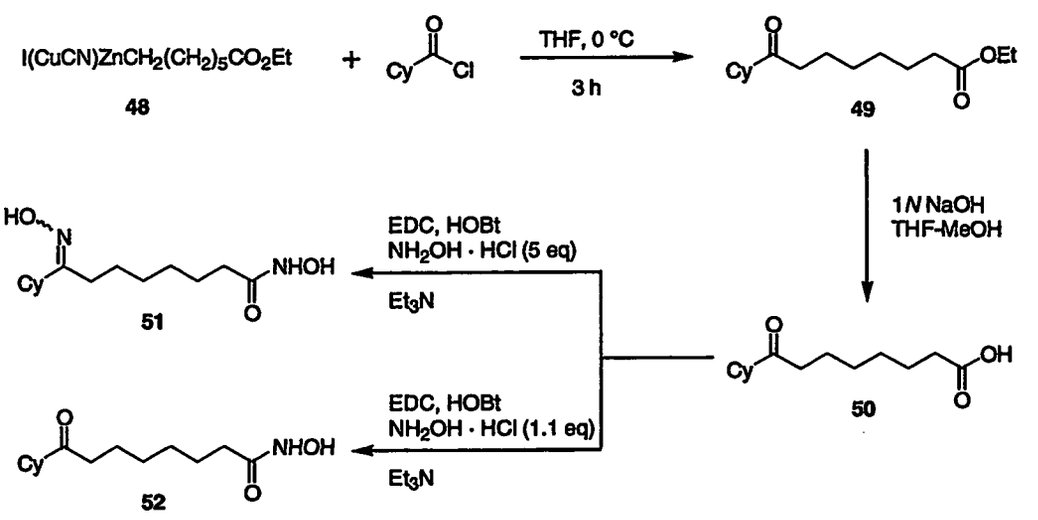
Step 2: 6-(benzenesulfonylamino)hexanoic acid (**46**)

[0160] Compound **46** was prepared in 69% yield, using the procedure described in Example 16, step 2, but substituting compound **45** for compound **40**. ^{1}H NMR: (300 MHz, acetone-d_6) δ 7.92-7.85 (m, 2H), 7.61-7.56 (m, 3H), 6.57 (br. s, 1H), 6.44 (br. s,1H), 2.94-2.88 (m, 2H), 2.26-2.21 (m, 2H), 1.55-1.46 (m, 4H), 1.38-1.33 (m, 2H).

Example 18:

***N*-Hydroxy-8-oximino-8-aryloctanamides (51) and *N*-Hydroxy-7-aroyl-heptanamides (52)**

[0161]



Step 1: Preparation of organocopper reagent **48**

[0162] To a suspension of zinc foil (3.40 g, 52 mmol) in THF (4 mL) was added 1,2-dibromoethane (0.38 g, 2.0 mmol), and the mixture was heated at 65 ˚C for one minute. After cooling to ambient temperature, chlorotrimethylsilane (0.2 mL, 1.6 mmol) was added and the mixture was stirred for 15 min. To this, a solution of ethyl 7-iodoheptanoate (14.21 g, 50 mmol) in THF (20 mL) was added slowly at ambient temperature, and the mixture was heated at 65 ˚C for 16 h and then cooled to -10 ˚C. A solution of CuCN (3.96 g, 44 mmol) and anhydrous LiCl (3.80 g, 88 mmol) in THF (44 mL) was added. The resulting solution was stirred at 0 ˚C for 10 min and used for the coupling reactions with acid chlorides.

Step 2: Ethyl 7-aroylheptanoates (**49**)

Ethyl 7-benzoylheptanoate (**49a**)

[0163] To a stirred solution of the organocopper reagent **48** (2.0 mmol) in THF (4 mL) at -25 ˚C was added benzoyl chloride (253 mg, 0.21 mmol) and the reaction mixture was warmed to 0 ˚C over 30min. After being stirred for additional 3 h at 0 ˚C, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography (10% ethyl acetate in hexanes) to afford the title compound (376 mg, 80% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 - 7.97 (m, 5H), 4.12(q, J = 6.9 Hz, 2H), 2.97 (t, J = 7.2 Hz, 2H), 2.30(t, J = 7.5 Hz, 2H), 1.74 (m, 2H), 1.65 (m, 2H), 1.39 (m, 4H), 1.25(t, J = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.19, 24.04, 24.75, 28.90(2), 34.12, 38.39, 60.11, 127.96, 128.49, 132.84, 136.95, 173.70, 200.29.

Ethyl 7-(*p*-anisoyl)heptanoate (**49b**)

[0164] Following a procedure analogous to that described above for 49a, but substituting *p*-anisoyl chloride for benzoyl chloride, the title compound was obtained as a light yellow solid in 59% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 4.12 (q, J = 6.9 Hz, 2H), 3.87 (s, 3H), 2.91 (t, J = 7.2 Hz, 2H), 230(t, J = 7.5 Hz, 2H), 1.74 (m, 2H), 1.65 (m, 2H), 1.39 (m, 4H), 1.25 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.19, 24.29,24.75,28.91,28.96,34.21,38.06,55.37, 60.10, 113.58, 130.02, 130.21, 163.23, 173.71, 198.93.

Ethyl 7-(4-(trifluoromethyl)benzoyl)heptanoate (**49c**)

[0165] Following a procedure analogous to that described above for **49a**, but substituting *p*-(trifluoromethyl)benzoyl chloride for benzoyl chloride, the title compound was obtained as a white solid in 67% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H), 4.13 (q, J = 6.9Hz, 2H), 3.01 (t, J = 7.2 Hz, 2H), 2.31 (t, J = 7.2 Hz, 2H), 1.76 (m, 2H), 1.66 (m, 2H), 1.41 (m, 4H), 1.25(t, J = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.00, 23.63, 24.56, 28.66, 28.71, 33.98, 38.48, 59.93, 123.46 (q, J_{CF} = 272 Hz), 125.42 (q, J_{CF} = 3.7Hz), 128.15, 133.93 (q, J_{CF} = 33.5 Hz), 139.52, 173.42, 198.91.

Ethyl 7-(4-bromobenzoyl)heptanoate (**49d**)

[0166] Following a procedure analogous to that described above for **49a**, but substituting *p*-bromobenzoyl chloride for benzoyl chloride, the title compound was obtained as a white solid in 70% yield: ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 4.12 (q, J = 6.9 Hz, 2H), 2.92 (t, J = 7.2 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.73 (m, 2H), 1.64 (m, 2H), 1.38 (m,4H),1.25 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.21, 23.95, 24.73, 28.87(2), 34.21, 38.37, 60.14, 127.98, 129.53, 131.82, 135.69, 173.66, 199.18.

Ethyl 7-(2-acetoxypenzoyl)heptanoate (**49e**)

[0167] Following a procedure analogous to that described above for **49a**, but substituting o-acetoxybenzoyl chloride for benzoyl chloride, the title compound was obtained as a colorless oil in 58% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, J = 8.4,1.5 Hz, 1H), 7.51 (m, 1H), 7.31 (m, 1H), 7.10 (dd, J = 7.8,1.2 Hz, 1H), 4.12(q, J = 6.9 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H), 2.33 (s, 3H), 2.29 (t, J = 7.5 Hz, 2H), 1.65 (m, 4H), 1.36 (m, 4H), 1.25(t, J = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.20, 21.07, 23.79, 24.73, 28.79, 28.87, 34.20, 40.18, 60.12, 123.77, 125.95, 129.60, 130.98,132.95, 148.74, 169.44, 173.66, 200.21.

Ethyl 7-(1-naphthoyl)heptanoate (**49f**).

[0168] Following a procedure analogous to that described above for **49a**, but substituting 1-naphthoyl chloride for benzoyl chloride, the title compound was obtained as a white solid in 58% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 8.7 Hz, 1H), 7.42-7.92 (m, 6H), 4.10 (q, J = 6.9 Hz, 2H), 2.98 (m, 2H), 2.26(t, J = 7.5 Hz, 2H), 1.75 (m, 2H), 1.62 (m, 2H), 1.36 (m, 4H), 1.22 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$)
δ 14.02, 24.23, 24.55, 28.70(2), 33.98, 1.79, 59.89, 124.12, 125.51, 126.12, 126.99, 127.51, 128.14, 129.87, 132.06, 133.69, 136.00, 173.39, 204.44.

Ethyl 7-(2-naphthoyl)heptanoate (**49g**)

[0169] Following a procedure analogous to that described above for **49a**, but substituting 2-naphthoyl chloride for benzoyl chloride, the title compound was obtained as a white solid in 54% yield: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.86-8.05 (m, 4H), 7.51-7.62 (m, 2H), 4.12 (q, J = 6.9 Hz, 2H), 3.10 (t, J = 7.5 Hz, 2H), 2.31 (t, J = 7.5 Hz, 2H), 1.80 (m, 2H), 1.62 (m, 2H), 1.41 (m, 4H), 1.25 (t, J = 6.9 Hz, 3H).

Ethyl 7-(4-biphenyl)carbonylheptanoate (**49h**)

[0170] Following a procedure analogous to that described above for **49a**, but substituting 4-biphenylcarbonyl chloride for benzoyl chloride, the title compound was obtained as a white solid in 41% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.2 Hz, 2H), 7.39-7.69 (m, 7H), 4.12 (q, J = 6.9 Hz, 2H), 2.99 (t, J = 7.2 Hz, 2H), 2.30(t, J = 7.5 Hz, 2H), 1.76 (m, 2H), 1.65 (m, 2H), 1.40 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H).

Ethyl 7-(2-furanoyl)heptanoate (**49i**)

[0171] Following a procedure analogous to that described above for **49a**, but substituting 2-furanoyl chloride, the title compound was obtained in 71% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 1.8 Hz, 1H), 7.19 (d, J = 3.3 Hz, 1H), 6.54 (dd, J = 3.3,1.8 Hz), 4.12 (q, J = 6.9 Hz, 2H), 2.82 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.72 (m, 2H), 1.64 (m, 2H), 1.38 (m, 4H), 1.25 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.07, 23.87, 24.58, 28.68, 28.72, 34.05, 38.14, 59.98, 111.97, 116.68, 146.05, 152.60, 173.52, 189.39.

Ethyl 7-(3-furanoyl)heptanoate (**49j**)

[0172] Following a procedure analogous to that described above for **49a**, but substituting 3-furanoyl chloride for benzoyl chloride, the title compound was obtained as a yellow oil in 24% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (m, 1H), 7.44 (m, 1H), 6.76 (m, 1H), 4.12 (q, J = 6.9 Hz, 2H), 2.74 (t, J = 7.5 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 1.71 (m, 2H), 1.63 (m, 2H), 1.37 (m, 4H), 1.25 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$)
δ 14.18, 24.04, 24.69, 28.82(2), 34.18, 40.23, 60.13, 108.56, 127.69, 144.09, 146.98, 173.68, 195.10.

Ethyl 7-(2-thiophene)carbonylheptanoate (**49k**)

[0173] Following a procedure analogous to that described above for **49a**, but substituting 2-thiophenecarbonyl chloride for benzoyl chloride, the title compound was obtained as a colorless oil in 66% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, J = 3.9,1.2 Hz,1H), 7.62 (dd, J = 4.8,1.2 Hz, 1H), 7.13 (dd, J = 4.8, 3.9Hz), 4.12(q, J = 7.2Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.75 (m, 2H), 1.64 (m, 2H), 1.39 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.23, 24.48, 24.75,
28.87, 28.90, 34.24, 39.23, 60.17, 128.01, 131.65, 133.34, 144.42, 173.73, 193.31.

Ethyl 7-(2-benzofulan)carbonylheptanoate (**491**)

[0174] Following a procedure analogous to that described above for **49a**, but substituting 2-benzofurancarbonyl chloride for benzoyl chloride, the title compound was obtained in 45% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.65 (m, 5H), 4.02 (q, J = 7.2 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H), 2.20(t, J = 7.5 Hz, 2H), 1.70 (m, 2H), 1.54 (m, 2H), 1.30 (m, 4H), 1.15 (t, J = 7.2 Hz, 3H).

Ethyl 7-(2-benzothiophene)carbonylheptanoate (**49m**)

[0175] Following a procedure analogous to that described above for 49a, but substituting 2-benzothiophenecarbonyl

chloride for benzoyl chloride, the title compound was obtained in 44% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.79 (m, 2H), 7.35 (m, 2H), 4.05 (q, J = 7.2 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 2.23 (t, J = 7.5 Hz, 2H), 1.70 (m, 2H), 1.57 (m, 2H), 1.30 (m, 4H), 1.19 (t, J = 7.2 Hz, 3H).

Step 3: 7-Aroylheptanoic acids (**50a-m)**

7-(2-Benzoyl)heptanoic acid (**50a**)

[0176] To a stirred solution of **49a** (610 mg, 2.3 mmol) in THF (3.5 mL) and MeOH (3.5 mL) at ambient temperature was added 1*N* NaOH (3.5 mL, 3.5 mmol), and the mixture was stirred for 2 h. After removal of organic solvents, the resulting aqueous solution was acidified with 1*N* HCl and then extracted with ethyl acetate. The combined organic layers were dried, concentrated under reduced pressure to give the crude product. Purification by flash silica gel chromatography (7% MeOH in chloroform) afforded the title compound (511 mg, 94% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 6.9 Hz, 2H), 7.41-7.61 (m, 3H), 2.97 (t, J = 7.5 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 1.75 (m, 2H), 1.66 (m, 2H), 1.40 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.01, 24.43, 28.80, 28.86, 33.92, 38.37, 127.98, 128.50, 132.88, 136.91, 179.95, 200.44.

7-(*p*-Anisoyl)heptanoic acid (**50b**)

[0177] Following a procedure described above in **50a**, but substituting ester **49b** for ester **49a**, the title compound was obtained as a white solid in 51% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 2.91(t, J = 7.5 Hz, 2H), 2.36(t, J = 7.5 Hz, 2H), 1.73 (m, 2H), 1.65 (m, 2H), 1.40 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$)
δ 24.25, 24.40, 28.76, 28.86, 33.83, 37.99, 55.33, 113.58, 129.93, 130.24, 163.26, 179.40, 199.22.

7-(4-Trifluoromethylbenzoyl)heptanoic acid (**50c**)

[0178] Following a procedure described above in **50a**, but substituting ester **49c** for ester **49a**, the title compound was obtained as a white solid in 68% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06(d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 3.00(t, J = 7.5 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 1.76(m, 2H), 1.67 (m, 2H), 1.42 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 23.75, 24.39, 28.78(2), 33.90, 38.67, 123.69(q, J_{CF} = 272 Hz), 125.62(q, J_{CF} = 3.7Hz), 128.33,134.21(q, J_{CF} = 32.6Hz), 139.59, 180.07, 199.28.

7-(4-Bromobenzoyl)heptanoic acid (**50d**)

[0179] Following a procedure described above in **50a**, but substituting ester **49d** for ester **49a**, the title compound was obtained as a white solid in 91% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 9.0 Hz, 2H), 2.93 (t, J = 7.5 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 1.74(m, 2H), 1.66(m, 2H), 1.40(m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 23.92, 24.43, 28.80, 28.84, 33.87, 38.35, 128.04, 129.56, 131. 85, 135.69, 179.74, 199.26.

7-(2-Acetoxybenzoyl)heptanoic acid (**50e**)

[0180] Following a procedure described above in **50a**, but substituting ester **49e** for ester **49a** and using 2.5 equivalent of 1*N* NaOH, the title compound was obtained as a white solid in 94% yield: ^{1}H NMR (300 MHz, $CDCl_3$):
δ 12.39 (s, 1H), 10.65 (br s, 1H), 7.75 (add, J = 8.1,1.5 Hz, 1H), 7.45 (m, 1H), 6.98 (dd, J = 8.4, 0.9 Hz, 1H), 6.89 (m, 1H), 2.98 (t, J = 7.5 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 1.76 (m, 2H), 1.66 (m, 2H), 1.41 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.13, 24.39, 28.75, 28.18, 33.90, 38.08, 118.47, 118.81, 119.25, 129.90, 136.18, 162.42, 180.04, 206.67.

7-(1-Naphthoyl)heptanoic acid (**50f**)

[0181] Following a procedure described above in **50a**, but substituting ester **49f** for ester **49a**, the title compound was obtained as a white solid in 97% yield: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (d, J = 8.7Hz, 1H), 7.95(d, J = 8.1Hz, 1H), 7.80-7.87 (m, 2H), 7.44-7.60 (m, 3H), 3.03 (t, J = 7.5 Hz, 2H), 2.34(t, J = 7.5Hz, ZH), 1.79(m, 2H), 1.64(m, 2H), 1.41(m, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 24.42(2), 28.80, 28.87, 33.92, 42.05, 124.31, 125.68, 126.35, 127.13, 127.75, 128.34, 130.05, 132.29, 133.90, 136.27,180.05,204.87.

7-(2-Naphthoyl)heptanoic acid (**50g**)

[0182] Following a procedure described above in **50a**, but substituting ester **49g** for ester **49a**, the title compound was obtained as a white solid in 78% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.85-8.05 (m, 4H), 7.57 (m, 2H), 3.10 (t, J = 7.5 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 1.80 (m, 2H), 1.67 (m, 2H), 1.43 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24:20, 24.48, 28.27, 28.95, 33.92, 38.48, 123.89, 126.69, 127.73, 128.33, 128.39, 129.52, 129.60, 132.51, 134.30, 135.50, 179.85, 200.36.

7-(4-Biphenyl)carbonylheptanoic acid (**50h**)

[0183] Following a procedure described above in **50a**, but substituting ester **49h** for ester **49a**, the title compound was obtained as a white solid in 93% yield: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, J = 9.0 Hz, 2H), 7.26-7.61 (m, 7H), 3.00 (t, J = 7.5 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 1.75 (m, 2H), 1.66 (m, 2H), 1.42 (m, 4H).

7-(2-Furanoyl)heptanoic acid (**50i**)

[0184] Following a procedure described above in **50a**, but substituting ester **49i** for ester **49a**, the title compound was obtained as a white solid in 88% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.4 (br s, 1H), 7.54 (d, J = 0.9 Hz, 1H), 7.15 (dd, J = 3.6,0.9 Hz, 1H), 6.49 (d, J = 3.6 Hz, 1H), 2.78 (t, J = 7.5 Hz, 2H), 2.31 (t, J = 7.5 Hz, 2H), 1.65 (m, 2H), 1.59 (m, 2H), 1.35 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 23.91, 24.32, 28.64, 28.73, 33.84, 38.16, 112.05, 116.89, 146.18, 152.61,179.81, 189.64.

7-(3-Furanoyl)heptanoic acid (**50j**)

[0185] Following a procedure described above in **50a**, but substituting ester **49j** for ester **49a**, the title compound was obtained as a white solid in 63% yield: ^{1}H NMR (300 MHz, $CDCl_3$ δ 8.03 (br s, 1H), 7.43 (m, 1H), 6.77 (d, J = 1.8 Hz, 1H), 2.74 (t, J = 7.5 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 1.72 (m, 2H), 1.65 (m, 2H), 1.38 (m,4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.02, 24.39, 28.74, 28.80, 33.88, 40.21, 108.58, 127.68, 144.12, 147.06, 179.84, 195.26.

7-(2-Thiophene)carbonylheptanoic acid (**50k**)

[0186] Following a procedure described above in **50a**, but substituting ester **49k** for ester **49a**, the title compound was obtained as a white solid in 77% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (dd, J = 3.6, 0.9 Hz, 1H), 7.62 (m, 1H), 7.12 (m, 1H), 2.90 (t, J = 7.5 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 1.75 (m, 2H), 1.65 (m, 2H), 1.40 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) : δ 24.31, 24.34, 28.64, 28.72, 33.83, 39.05, 127.96, 131.72, 133.37, 144.20, 179.92, 193.35.

7-(2-Benzofuran)carbonylheptanoic acid (**501**)

[0187] Following a procedure described above in **50a**, but substituting ester **491** for ester **49a**, the title compound was obtained as a white solid in 84% yield: ^{1}H NMR (300 MHz, acetone-d_6) δ 10.6 (br s, 1H), 7.25-7.80 (m, 5H), 3.00 (t, J = 7.5 Hz, 2H), 2.24 (t, J = 7.5 Hz, 2H), 1.60-1.80 (m, 4H), 1.40 (m, 4H).

7-(2-Benzothiophene)carbonylheptanoic acid (**50m**)

[0188] Following a procedure described above in **50a**, but substituting ester **49m** for ester **49a**, the title compound was obtained as a white solid in 90% yield: ^{1}H NMR (300 MHz, acetone-d_6) δ 10.5(br s, 1H), 7.40-8.25 (m, 5H), 3.10 (t, J = 7.5 Hz, 2H), 2.14 (t, J = 7.5 Hz, 2H), 1.50-1.80 (m, 4H), 1.40 (m, 4H).

Step 4: *N*-Hydroxy-8-oximino-8-aryloctanamides (**51**) and *N*-Hydroxy-7-aroyl-heptanamides (**52a-m**)

N-Hydroxy-8-oximino-8-phenyloctanamide (**51a**)

[0189] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50a** for **37**, the title compound was obtained as light yellow oil in 54% yield: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 7.55 (m, 2H), 7.36 (m, 3H), 2.79 (t, J = 7.5 Hz, 2H), 2.07 (t, J = 7.5 Hz, 2H), 1.56 (m, 4H), 1.35 (m, 4H); ^{13}C NMR (75.4 MHz, CD_3OD /$CDCl_3$ = 5/1)
δ 25.09, 25.78, 25.92, 28.43, 28.95, 32.55,126.12, 128.21, 128.75, 135.85, 159.52, 171.25.

N-Hydroxy-8-(*E*)-oximino-8-(4-biphenyl)octanamide (***E*-51h**) and *N*-Hydroxy-8-(*Z*)-oximino-8-(4-biphenyl)octanamide (**Z-51h**)

[0190] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50h** for **37** the title compound **51h** was obtained as a white solid in 45% yield, along with **52h** (19%). Data for 51h: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 7.25-7.67(m, 9H), 7.36 (m, 3H), 2.82 (t, J = 7.5 Hz, 2H), 2.06 (br t, J = 6.9 Hz, 2H), 1.59 (m, 4H), 1.37 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$ /$CDCl_3$ = 5/1) δ 25.13, 25.78, 25.88, 28.47, 29.00, 32.58, 126.51, 126.72, 126.85, 127.33, 128.59, 134.72, 140.14, 141.47, 159.17,171.24. Data for 52h: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 7.35-7.68 (m, 9H), 2.83 (t, J = 7.8 Hz, 2H), 2.29(t, J =7.5 Hz, 2H), 1.62 (m, 2H), 1.60 (m, 2H), 1.40 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$ /$CDCl_3$ = 5/1) δ 24.55, 25.92, 28.58(2), 29.29, 33.79, 126.52, 126.75, 126.86, 127.31, 128.58, 134.76, 140.17, 141.46, 159.20, 176.54.

N-Hydroxy-8-oximino-8-(2-furanyl)octanamide (**51i**) and *N*-hydroxy-7-(2-furanoyl)heptanamide (**52i**)

[0191] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50i** for **37,** the title compound **51i** was obtained as a 6:4 mixture of *E*- and Z-isomers in 26% yield, along with **52i** (11%). Data for **51i**: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 6.31-7.35 (m, 3H), 2.50 (m, 2H), 1.98 (m, 2H), 1.47 (m, 4H), 1.24 (m, 4H). Data for **52i**: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 7.61 (d, J =1.2 Hz, 1H), 7.21 (d, J = 3.3 Hz, 1H), 6.55 (dd, J = 3.3,1.2 Hz, 1H), 2.82 (t, J = 7.5 Hz, 2H), 2.10 (t, J = 7.5 Hz, 2H), 1.60-1.72 (m, 4H), 1.36 (m, 4H); ^{13}C NMR (75.4 MHz, CD_3OD /$CDCl_3$ = 5/1) δ 23.84, 25.00, 28.49(2), 32.47, 37.98, 112.08, 117.45, 146.53, 152.27, 171.09, 190.25.

N-hydroxy-7-benzoylheptanamide (**52a**)

[0192] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50a** for **37** and using 1.1 equivalent of $NH_2OH \cdot HCl$ and triethylamine each, the title compound was obtained as light yellow solid in 46% yield: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1): δ 7.95 (d, J = 7.2 Hz, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 2.98 (t, J = 7.5 Hz, 2H), 2.13 (m, 2H), 1.72 (m, 2H), 1.64 (m, 2H), 1.38 (m, 4H); ^{13}C NMR (75.4 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 23.77, 24.98, 28.49(2), 32.49, 38.13, 127.73, 128.29, 132.86, 136.46, 171.23, 201.16.

N-hydroxy-7-(*p*-anisoyl)heptanamide (**52b**)

[0193] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50b** for **37** and using 1.1 equivalent of $NH_2OH \cdot HCl$ and triethylamine each, the title compound was obtained as light yellow solid in 48% yield: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 7.94 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 3.88 (s, 3H), 2.93 (t, J = 7.2 Hz, 2H), 2.11 (t, J = 7.5 Hz, 2H), 1.59-1.79(m, 4.H), 1.37 (m, 4H); ^{13}C NMR (75.4 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 24.15, 25.04, 28.59(2), 32.51, 37.88, 55.21, 113.54, 129.58, 130.20, 163.39, 171.10, 200.06.

N-hydroxy-7-(4-trifluoromethylbenzoyl)heptanamide(**52c**)

[0194] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50c** for **37** and using 1.1 equivalent of $NH_2OH \cdot HCl$ and triethylamine each, the title compound was obtained as light yellow solid in 35% yield: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 8.07 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 3.02 (t, J = 7.5 Hz, 2H), 2.12 (t, J = 7.5 Hz, 2H), 1.75 (m, 2H), 1.65 (m, 2H), 1.40 (m, 4H); ^{13}C NMR (75.4 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 23.57, 25.03, 28.51, 28.59, 32.50, 38.50, 123.37(q, J_{CF} = 273 Hz),125.43 (q, J_{CF} = 3.7 Hz), 128.18, 134.09 (q, J_{CF} = 32.6 Hz), 139.32, 171.15, 199.93.

N-hydroxy-7-(4-bromobenzoyl)heptanamide (**52d**)

[0195] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50d** for **37** and using 1.1 equivalent of $NH_2OH \cdot HCl$ and triethylamine each, the title compound was obtained as light yellow solid in 31% yield: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 7.82 (d, J = 7.5 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 2.95 (t, J = 7.2 Hz, 2H), 2.11 (m, 2H), 1.55-1.79 (m, 4H), 1.38 (m, 4H).

N-hydroxy-7-(2-acetoxybenzoyl)heptanamide (**52e**)

[0196] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50e** for **37** and using 1.1 equivalent of $NH_2OH \cdot HCl$ and triethylamine each, the title compound was obtained as light yellow solid in 43%

yield: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 7.78 (dd, J = 8.1,1.2 Hz, 1H), 7.47 (m, 1H), 6.96 (dd, J = 8.4,1.2 Hz, 1H), 6.91 (m, 1H), 3.00 (t, J = 7.2 Hz, 2H), 2.12 (t, J = 7.5 Hz, 2H), 1.59-1.79 (m, 4H), 1.40 (m, 4H); ^{13}C NMR (75.4 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 23.97, 32.51, 37.94, 118.02, 118.84, 119.01, 129.86, 136.09, 161.76,171.15,206.79.

N-hydroxy-7-(1-naphthoyl)heptanamide (**52f**)

[0197] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50f** for **37** and using 1.1 equivalent of $NH_2OH \cdot HCl$ and triethylamine each, the title compound was obtained as light yellow solid in 58% yield: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 8.50 (d, J = 8.1 Hz, 1H), 7.40-7.90 (m, 6H), 293(t, J = 7.5 Hz, 2H), 2.12 (m, 2H), 1.69 (m, 2H), 1.59 (m, 2H), 1.30 (m, 4H); ^{13}C NMR (75.4 MHz, $CD_3OD/CDCl_3$ = 5/1) 8 24.27, 25.08, 28.63 (2), 32.65, 41.88, 124.29, 125.53, 126.27, 127.33, 127.70, 128.30, 129.91, 132.32, 133.77, 135.91, 171.87,205.28.

N-hydroxy-7-(2-naphthoyl)heptanamide (**52g**)

[0198] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50g** for **37** and using 1.1 equivalent of $NH_2OH \cdot HCl$ and triethylamine each, the title compound was obtained as light yellow solid in 31% yield: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 8.47 (s, 1H), 7.53-8.01 (m, 6H), 3.10 (t, J = 7.5 Hz, 2H), 2.12 (m, 2H), 1.78 (m, 2H), 1.66 (m, 2H), 1.42 (m, 4H); ^{13}C NMR (75.4 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 24.01, 25.07, 28.62(2), 32.54, 38.27, 123.47, 126.56, 127.48, 128.22, 128.28, 129.03, 129.60, 132.27, 133.86, 135.37, 171.19, 201.18.

N-hydroxy-7-(3-furanoyl)heptanamide (**52j**)

[0199] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50j** for **37** and using 1.1 equivalent of $NH_2OH \cdot HCl$ and triethylamine each, the title compound was obtained as light yellow solid in 33% yield: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 8.09 (br s, 1H), 7.46 (m, 1H), 6.75 (m, 1H), 2.76 (t, J = 7.5 Hz, 2H), 2.10 (t, J = 7.5 Hz, 2H),1.60-1.72 (m, 4H),1.36 (m, 4H); ^{13}C NMR (75.4 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 23.90, 24.99, 28.45 (2), 32.48, 39.98, 108.19, 127.37, 144.15, 147.43, 171.08, 196.21.

N-hydroxy-7-(2-thiophene)carbonylheptanamide (**52k**)

[0200] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50k** for **37** and using 1.1 equivalent of $NH_2OH \cdot HCl$ and triethylamine each, the title compound was obtained as light yellow solid in 56% yield: ^{1}H NMR (300 MHz, CD_3OD/CDI_3 = 5/1) 8 7.76 (d, J = 2.7 Hz, 1H), 7.68 (d J =4.5 Hz, 1H), 7.16 (m, 1H), 2.92(t, J = 7.5 Hz, 2H), 2.10 (t, J = 7.5 Hz, 2H), 1.74 (m, 2H), 1.64 (m, 2H), 1.36 (m, 4H).

N-hydroxy-7-(2-benzofuran)carbonylheptanamide (**521**)

[0201] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **501** for **37** and using 1.1 equivalent of $NH_2OH \cdot HCl$ and triethylamine each, the title compound was obtained as light yellow solid in 20% yield: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.35-7.85 (m, 5H), 2.99 (t, J = 7.5 Hz, 2H), 2.10(t, J = 7.5 Hz, 2H), 1.50-1.80 (m, 4H), 1.36 (m, 4H).

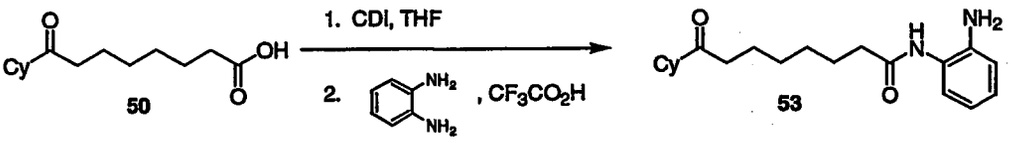
N-hydroxy-7-(2-benzothiophene)carbonylheptanamide (**52m**)

[0202] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50m** for **37** and using 1.1 equivalent of $NH_2OH \cdot HCl$ and triethylamine each, the title compound was obtained as light yellow solid in 31% yield: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 8.23 (s, 1H), 8.00 (m, 2H), 7.49 (m, 2H), 3.05 (t, J = 7.5 Hz, 2H), 2.10 (t, J = 7.5 Hz, 2M, 1.50-1.80 (m, 4H), 1.40 (m, 4H).

Example 19:

N-(2-Aminophenyl)-7-aroylheptanamides (53)

[0203]



N-(2-Aminophenyl)-7-benzoylheptanamide (**53a**)

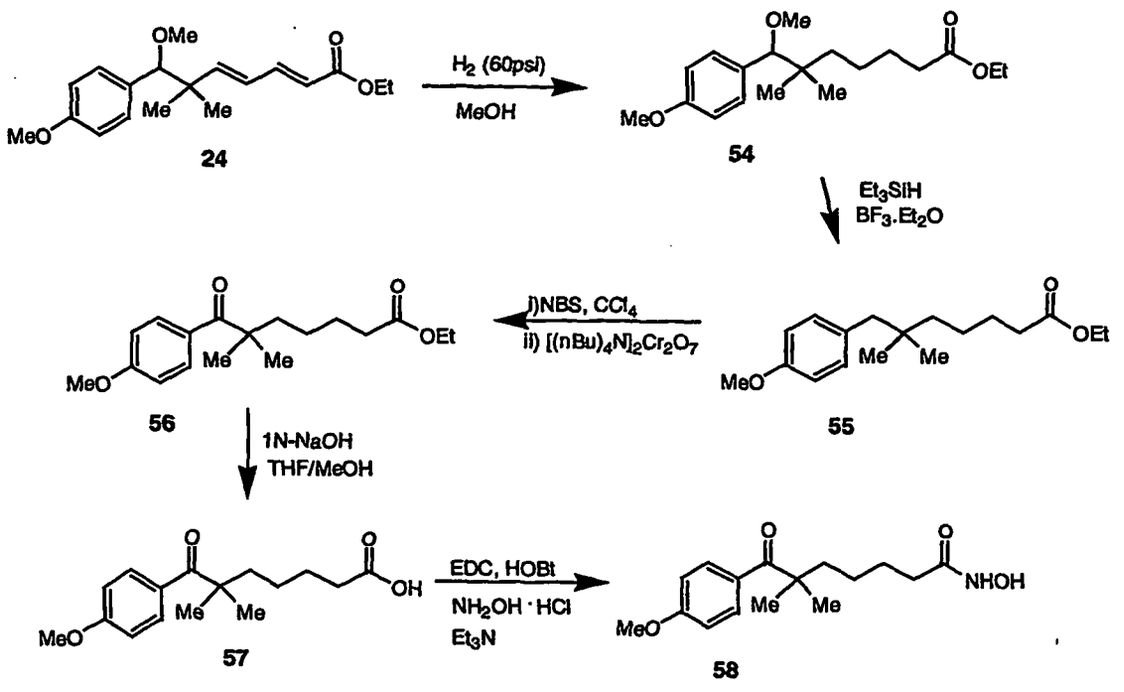
[0204] Following the procedure described in Example 6, but substituting carboxylic acid **50a** for **16**, the title compound was obtained in 23% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 8.4 Hz, 2H), 7.82 (br s, 1H), 6.70-7.55 (m, 7H), 3.90 (br s, 2H), 2.94 (t, J = 7.5 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 1.60-1.80 (m, 4H), 1.43 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 23.94, 25.47, 28.79, 28.87, 36.49, 38.29, 117.78, 119.01, 124.16, 125.36, 126.89, 127.90, 128.45, 132.87, 136.80, 140.88, 172.07, 200.52.

N-(2-Aminophenyl)-7-(*p*-anisoyl)heptanamide (**53b**)

[0205] Following the procedure described in Example 6, but substituting carboxylic acid **50b** for **16**, the title compound was obtained in 40% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 8.7 Hz, 2H), 7.35 (br s, 1H), 7.19 (m, 1H), 7.05 (m, 1H), 6.92 (d, J = 8.7 Hz, 2H), 6.70-6.80 (m, 2H), 3.86 (s, 3H), 3.85 (br s, 2H), 2.92 (t, J = 7.5 Hz, 2H), 2.40 (t, J = 7.5 Hz, 2H), 1.65-1.80 (m, 4H), 1.43 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.23, 25.56, 28.88, 28.92, 37.00, 38.03, 55.43, 113.67, 118.13, 119.43, 124.37, 125.18, 127.05, 130.06, 130.29, 140.78, 163.34, 171.82, 199.13.

N-(2-Aminophenyl)-7-(1-naphthoyl)heptanamide (**53f**)

[0206] Following the procedure described in Example 6, but substituting carboxylic acid **50f** for **16**, the title compound was obtained in 60% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, J = 7.8 Hz, 1H), 8.05 (br s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 6.60-7.82 (m, 9H), 3.69 (br s, 2H), 2.94 (t, J = 7.5 Hz, 2H), 2.18 (t, J = 7.5 Hz, 2H), 1.55-1.80 (m, 4H), 1.28 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$)
δ 24.20, 25.30, 28.64, 28.69, 36.16,41.78, 117.37,
118.62, 123.87, 124.14, 125.35, 125.42, 126.13, 126.70, 127.06, 127.52, 128.18, 129.74, 132.13, 133.61, 135.85, 140.89,172.15, 204.96.



Example 20:

***N*-Hydroxy-6,6-dimethyl-7-(4-methoxybenzoyl)heptanamide (58)**

Step 1: Ethyl 6,6-dimethyl-7-methoxy-7-(4-methoxyphenyl)-heptanoate (**54**)

[0207] Following the procedure described in Example 10, step1, but substituting ester **24** for carboxylic acid **16**, the title compound was obtained in 94% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.12(q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 1H), 3.15 (s, 3H), 2.30 (t, J = 7.2 Hz, 2H), 1.59 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 1.25-1.40 (m, 4H), 0.83 (s, 3H), 0.76 (s, 3H).

Step 2: Methyl 6,6-dimethyl-7-(4-methoxyphenyl)heptanoate-(**55**)

[0208] Following the procedure described in Example 14, step1, but substituting ester **54** for ester **31,** the title compound was obtained in 64% yield. ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.01 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 2.43 (s, 2H), 2.31 (t, J = 7.2 Hz, 2H), 1.60 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 1.15-1.40 (m, 4H), 0.82 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$)
δ 14.26, 23.76, 25.81, 26.69, 34.07,
34.41, 41.50, 47.40, 55.16, 60.16, 113.01, 131.37, 131.40, 157.73, 173.83.

Step 3: Ethyl 6-Methyl-6-(4-methoxybenzoyl)heptanoate (**56**)

[0209] A mixture of ester **55** (190 mg, 0.65 mmol) and *N*-bromosuccinimide(150 mg, 0.85 mmol) in CCl_4 was heated at reflux overnight in the presence of a catalytic amount of AIBN (7mg). The reaction mixture was cooled to ambient temperature, and the floating solid was filtered off. The filtrate was then concentrated to give the crude benzylic bromide: ^{1}H NMR (300 MHz, $CDCl_3$)
δ 7.28 (d, J = 8.7 Hz, 2H), 6.81(d, J = 8.7 Hz, 2H), 4.89 (s, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.80 (s, 3H), 2.31 (t, J = 7.5 Hz, 2H), 1.60 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 1.10-1.40 (m, 4H), 1.05 (s, 3H), 0.93 (s, 3H).

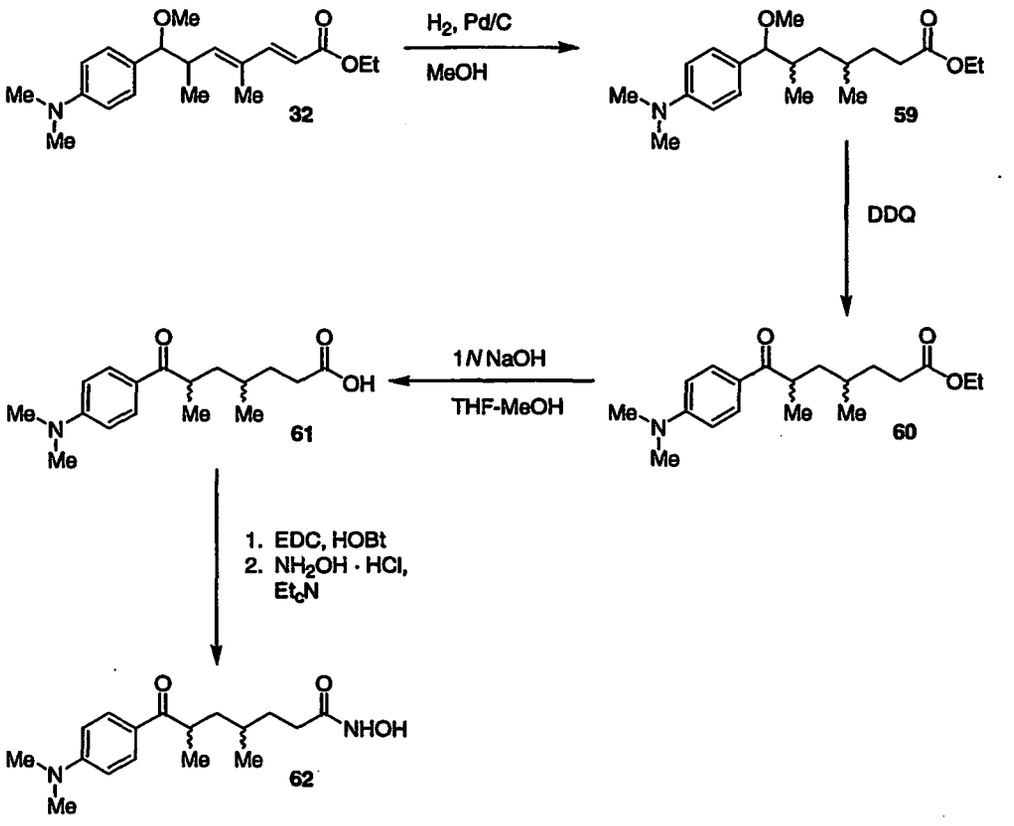
[0210] A mixture of crude bromide obtained above and bis(tetrabutylammonium)dichromate (1.68 g, 2.4 mmol) was heated at reflux in $CHCl_3$ (10 mL) for 4 h. After removal of the solvent, the residue was dissolved in ethyl ether (50 mL), washed with water, dried and concentrated. Purification by flash silica gel chromatography (15% ethyl acetate in hexanes) gave the title compound (230 mg, 63% yield) as light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$)
δ 7.81 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 4.08 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 2.23 (t, J = 7.5 Hz, 2H), 1.79 (m, 2H), 1.55 (m, 2H), 1.32 (s, 6H), 1.23 (t, J = 7.2 Hz, 3H), 1.21 (m, 2H).

Step 4: 6-Methyl-6-(4-methoxybenzoyl)heptanoic acid (**57**)

[0211] Following a procedure analogous to that described for **50a** but substituting ester **56** for ester **49a,** the title compound was obtained in 93% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 3.73 (s, 3H), 2.10 (t, J = 7.5 Hz, 2H), 1.67 (m, 2H), 1.42 (m, 2H), 1.19 (s, 6H), 1.13 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.15, 25.13, 26.16, 33.57, 40.81, 47.32, 55.08, 113.11, 130.27, 130.31, 161.90,176.12,207.01.

Step 5: *N*-Hydroxy-6-me+yl-6-(4-methoxybenzoyl)-heptanamide (**58**)

[0212] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **57** for **37,** the title compound was obtained in 39% yield: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1): 7.80 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 2.05 (t, J = 7.5 Hz, 2H), 1.77 (m, 2H), 1.47 (m, 2H), 1.32 (s, 6H), 1.23 (m, 2H); ^{13}C NMR (75.4 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 24.14,25.71,26.17,29.40,32.40, 40.75, 55.08, 113.12, 130.15, 130.32, 161.94, 170.94, 207.08.



Example 21:

***N*-Hydroxy-4,6-dimethyl-6-[4-(*N*,*N*-dimethyl)benzoyl]heptanamide(62)**

Step 1: Ethyl 4,6-dimethyl-7-methoxy-7-[4-(*N,N*-dimethylamino)phenyl]heptanoic acid -(**59**)

[0213] Following the procedure described in Example 10, step1, but substituting ester **32** for carboxylic acid **16**, the title compound was obtained as an inseparable mixture of isomers in 99% yield: **major isomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d,J = 9.0 Hz, 2H), 6.70(d, J=9.0Hz, 2H),4.10(q,J=7.2Hz, 2H), 3.74 (d,J =6.9 Hz, 1H), 3.16 (s, 3H), 2.95 (s, 6H), 2.21 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H), 1.00-1.83 (m, 6H), 0.90 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.0 Hz, 3H).

Step 2: Ethyl 4-methyl-6-[4-(*N,N*-dimethylamino)benzoyl]heptanoate (**60**)

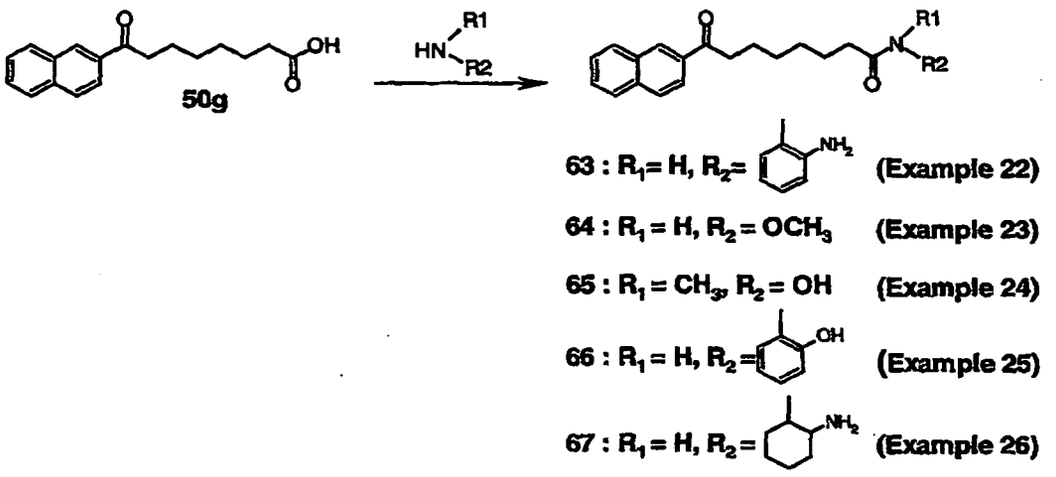
[0214] Following the procedure described in Example 13, but substituting ester **59** for compound **34**, the title compound was obtained as a ca. 3:1 mixture of isomers in 42% yield: **major isomer** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 9.0 Hz, 2H), 6.64 (d, J = 9.0 Hz, 2H), 4.18 (q, J =7.2 Hz, 2H), 3.45 (m, 1H), 3.05 (s, 6H), 2.13 (m, 2H), 1.22(t, J = 7.2 Hz, 3H), 1.20-1.83 (m, 5H), 1.02 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) 814.13, 17.53, 19.02, 30.33, 31.80, 32.16, 37.06, 39.91, 40.06, 60.08, 110.66, 124.15, 130.32, 153.19, 173.81, 202.28.

Step 3: 4-Methyl-6-[4-(*N,N*-dimethylamino)benzoyl]heptanoic acid (**61**)

[0215] Following the procedure described for **50**, but substituting ester **60** for ester **49**, the title compound was obtained in 94% yield: **major isomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 9.0 Hz, 2H), 6.66 (d, J = 9.0 Hz, 2H), 3.45 (m, 1H), 3.05 (s, 6H), 2.15 (m, 2H), 1.20-1.83 (m, 5H), 1.14 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.3 Hz, 3H).

Step 4: *N*-Hydroxy-4-Methyl-6-[4-(*N,N*-dimethylamino)benzoyl]heptanamide (**62**)

[0216] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **61** for **37**, the title compound was obtained in 44% yield: **major isomer**: ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$ = 5/1) δ 7.82 (d, J = 9.0 Hz, 2H), 6.62 (d, J = 9.0 Hz, 2H), 3.40 (m, 1H), 3.01(s, 6H), 2.05 (m, 2H), 1.20-1.83 (m,5H), 1.07 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.3Hz, 3H).



[0217] Example 23,24 and 26 are for illustration purpose only.

Example 22

***N*-(2-Aminophenyl)-7-(2-naphthoyl)heptanamide (63)**

[0218] To a solution of 7-(2-naphthoyl)heptanoic acid **50g** (1.00 g, 3.52 mmol) in DMF (15 mL) were added HOBT (950 mg, 7.04 mmol) and EDC (1.00 g, 5.28 mmol). The mixture was stirred at room temperature for 1 hour, after which 1,2-phenylenediamine (760 mg, 7.04 mmol) was added and the solution was stirred at room temperature for 16 hours. The DMF was evaporated under high vacuum, deionized water was added, and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with saturated sodium bicarbonate (20 mL), washed with brine (20 mL), and dried ($MgSO_4$). The solvents were removed *in vacuo* and the title compound **63** (558 mg, 42%) was isolated by recrystallization from acetone and dichloromethane. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 8.47 (s, 1H), 8.10-7.85 (m, 4H), 7.63-7.50 (m, 2H), 7.14-6.70 (m, 4H), 3.11 (t, J = 7.2 Hz, 2H), 239 (t, J = 7.5 Hz, 2H), 1.77 (m, 4H), 1.46 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$): δ 23.99, 25.40, 28.66, 28.74, 36.08, 38.23,117.69,119.09,123.45,124.01,125.34,126.53126.86,127.45, 128.19, 128. 23,129.28, 129.56, 32.23,133.85, 135.32, 140.58, 172.81, 201.11.

Example 23:

***N*-Methoxy-7-(2-naphthoyl)heptanamide (64)**

[0219] To a solution of 7-(2-naphthoyl)heptanoic acid **50g** (500 mg, 1.76 mmol) in DMF (10 mL) were added HOBT (309 mg, 2.29 mmol) and EDC (504 mg, 2.64 mmol). The mixture was stirred at room temperature for 1 hour, after which methoxylamine-HCl (176 mg, 2.11 mmol) and triethylamine (300 μL, 2.11 mmol) were added and the solution was stirred at room temperature for 16 hours, then at 45°C for 2 hours. The DMF was evaporated under high vacuum, deionized water was added, and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with saturated sodium bicarbonate (10 mL), washed with brine (10 mL), and dried ($MgSO_4$). The solvents were removed *in vacuo* and the title compound **64** (308 mg, 56%) was isolated by recrystallization from acetone. ^{1}H NMR (400 MHz, 5:1 $CDCl_3$:CD_3OD): 8.37 (s, 1H), 7.89 (m, 2H), 7.78 (m, 2H), 7.48 (m, 2H), 3.59 (s, 3H), 3.01 (t, J = 7.3 Hz, 2H), 1.96 (t, J = 7.3 Hz, 2H), 1.67 (m, 2H), 1.54 (m, 2H), 1.31 (m, 4H).

Example 24:

***N*-Hydroxy-*N*-methyl-7-(2-naphthoyl)heptanamide (65)**

[0220] Following the procedure described in Example 23, but substituting *N*-methyl-hydroxylamine-HCl for methoxylamine-HCl, the title compound 65 was obtained in 34% yield. ^{1}H NMR (400 MHz, 5:1 $CDCl_3$:CD_3OD): δ 8.37 (s, 1H), 7.88 (m, 2H), 7.78 (m, 2H), 7.47 (m, 2H), 3.10 (s, 3H), 3.01 (t, J = 7.1 Hz, 2H), 2.36 (t, J = 6.5 Hz, 2H), 1.67 (m, 2H), 1.52 (m, 2H),1.32 (m, 4H).

Example 25:

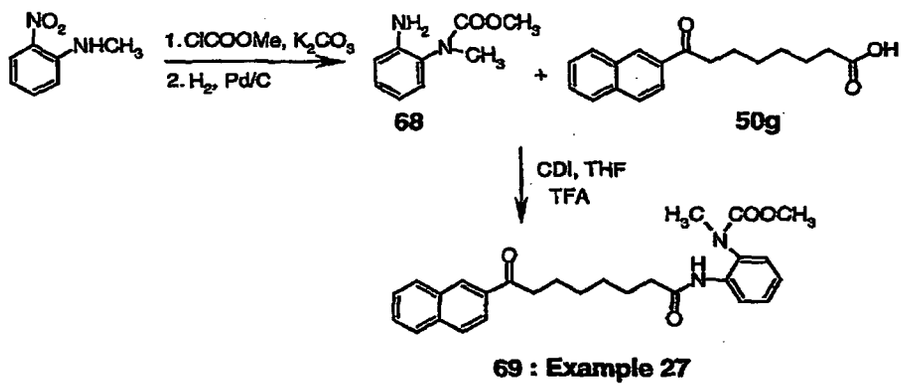
***N*-(2-Hydroxyphenyl)-7-(2-naphthoyl)heptanamide (66)**

[0221] Following the procedure described in Example 22, but substituting 2-aminophenol for 1,2-phenylenediamine, the title compound **66** was obtained in 20% yield after purification by flash silica gel chromatography (3% methanol in dichloromethane) followed by crystallization in ethyl acetate. ^{1}H NMR ($CDCl_3$): δ 8.38 (s, 1H), 7.89 (m, 2H), 7.81 (m, 2H), 7.48 (m, 3H), 6.81 (m, 3H), 3.03 (t, J = 7.3 Hz, 2H), 2.34 (t, J = 7.5 Hz, 2H), 1.68 (m, 4H), 1.37 (m, 4H).

Example 26:

***N*-(2-Aminocyclohexyl)-7-(2-naphthoyl)heptanamide (67)**

[0222] Following the procedure described in Example 6, but substituting the carboxylic acid **50g** for the carboxylic acid **16** and 1,2-diaminocyciclohexyl for 1,2-phenylenediamine, the title compound **67** was obtained in 16% yield. ^{1}H NMR (300MHz, $CDCl_3$: δ 8.44 (s, 1H). 8.0-7.82 (m, 4H), 7.65-7.48 (m, 3H), 3.80-3.70 (br s, 2H), 3.07 (t, J = 6.9 Hz, 2H), 1.20-2.25 (m, 20H).



69 : Example 27

[0223] Example 27 is for illustration purpose only.

Example 27:

***N*-(2-(*N*-Methyl-N-methyloxycarbonyl)aminophenyl)-7-(2-naphthoyl)heptanamide (69)**

Step 1: 2-(*N*-Methyl-*N*-methyloxycarbonyl)aminoaniline (**68**)

i) Substitution reaction

[0224] To a solution of *N*-methyl-2-nitroaniline (1.00 g, 6.58 mmol) in acetone (15 mL) was added methyl chloroformate (2.0 mL, 26 mmol) and potassium carbonate (5.45 g, 39.5 mmol). The reaction mixture was refluxed for 16 hours and then stirred at room temperature for 96 hours. The acetone was removed *in vacuo,* water was added, and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvents were removed *in vacuo* and the compound (808 mg, 59%) was isolated by column chromatography (25% to 40% of ethyl acetate in hexane). ^{1}H NMR: (400MHz, DMSO-d_6): δ 8.02 (m, 1H), 7.78 (m, 1H), 7.63 (d, J = 7.7 Hz,

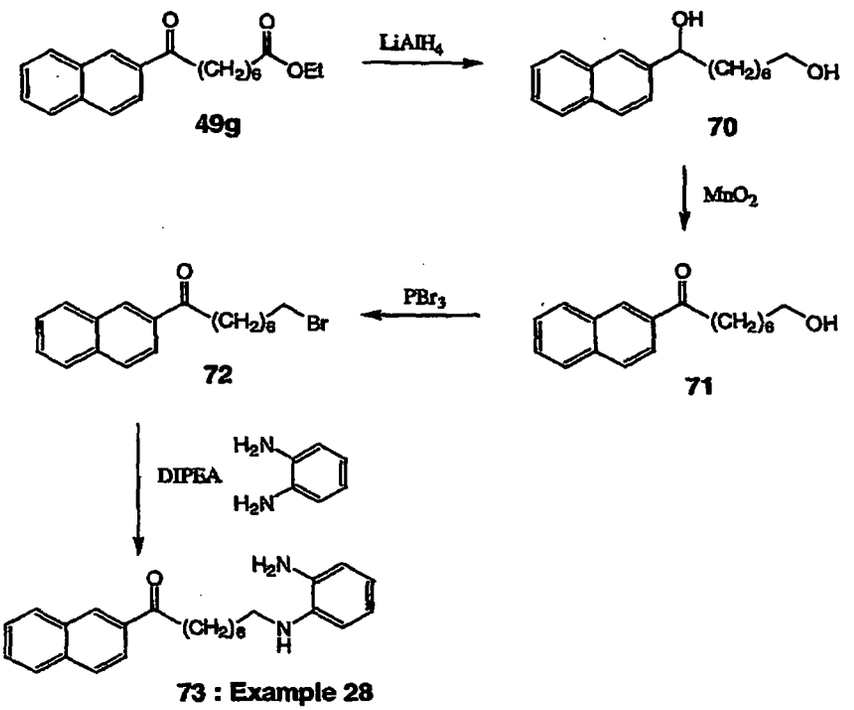
1H), 7.55 (m, 1H), 3.66 and 3.45 (s, 3H), 3.29 and 3.23 (s, 3H).

ii) Hydrogenation

[0225] A solution of 2-(*N*-methyl-*N*-methyloxycarbonyl)nitroaniline (600 mg, 2.86 mmol) in methanol (6 mL) was hydrogenated over 10% Pd/C (51 mg, 0.048 mmol) for 2 hours. The reaction mixture was filtered through a short pad of Celite and the solvent was removed *in vacuo* to give the title compound **68** (489 mg, 95%). ^{1}H NMR (400MHz, DMSO-d_6): δ 6.94 (m, 2H), 6.70 (m, 1H), 6.50 (m, 1H), 5.01 (br s, 2H), 3.64 and 3.49 (s, 3H), 3.33 (s, 3H).

Step 2: *N*-(2-(*N*-Methyl-*N*-methyloxycarbonyl)aminophenyl)-7-(2-naphthoyl)-heptanamide (**69**)

[0226] Following the procedure described in Example 6, but substituting the carboxylic acid **50g** for the carboxylic acid **16** and the *N*-methyl, *N*-methyloxycarbonyl-1,2-phenylenediamine for 1,2-phenylenediamine, the title compound **69** was obtained in 32% yield. MS (ESI) = 447.5 (MH^+)



[0227] Example 28 is for illustration purpose only.

Example 28:

***N-(2-Aminophenyl)-7-(2-naphthoyl)heptanamine* (73)**

Step 1:1-Hydroxy-1-[(2-naphthyl)]-8-octanol (**70**)

[0228] Lithium aluminum hydride (114 mg, 3.00 mmol) was added to diethyl ether (3 mL) at 0˚C. A solution of ethyl-7-(2-naphthoyl)-heptanoate **49g** (312 mg, 1.00 mmol) in ether (2 mL) was added dropwise at 0˚C and the reaction mixture was stirred at 0˚C for 1 hour, then at room temperature for 1 hour. Deionized water was added slowly dropwise (5 mL) followed by 2N NaOH (5 mL). The mixture was filtered through a short pad of Celite, washing with ether. The organic layer was separated and dried ($MgSO_4$). The solvents were removed *in vacuo* to give the title compound 70 (247 mg, 91%). ^{1}H NMR (400 MHz, DMSO-d_6:
δ 7.83 (m 4H), 7.45 (m, 3H), 5.22 (m, 1H), 4.64 (m, 1H), 4.28 (m, 1H), 3.35 (m, 2H), 1.68 (m, 2H), 1.37 (m, 2H), 1.22 (m, 8H).

Step 2: 7-(2-Naphthoyl)-1-heptanol (**71**):

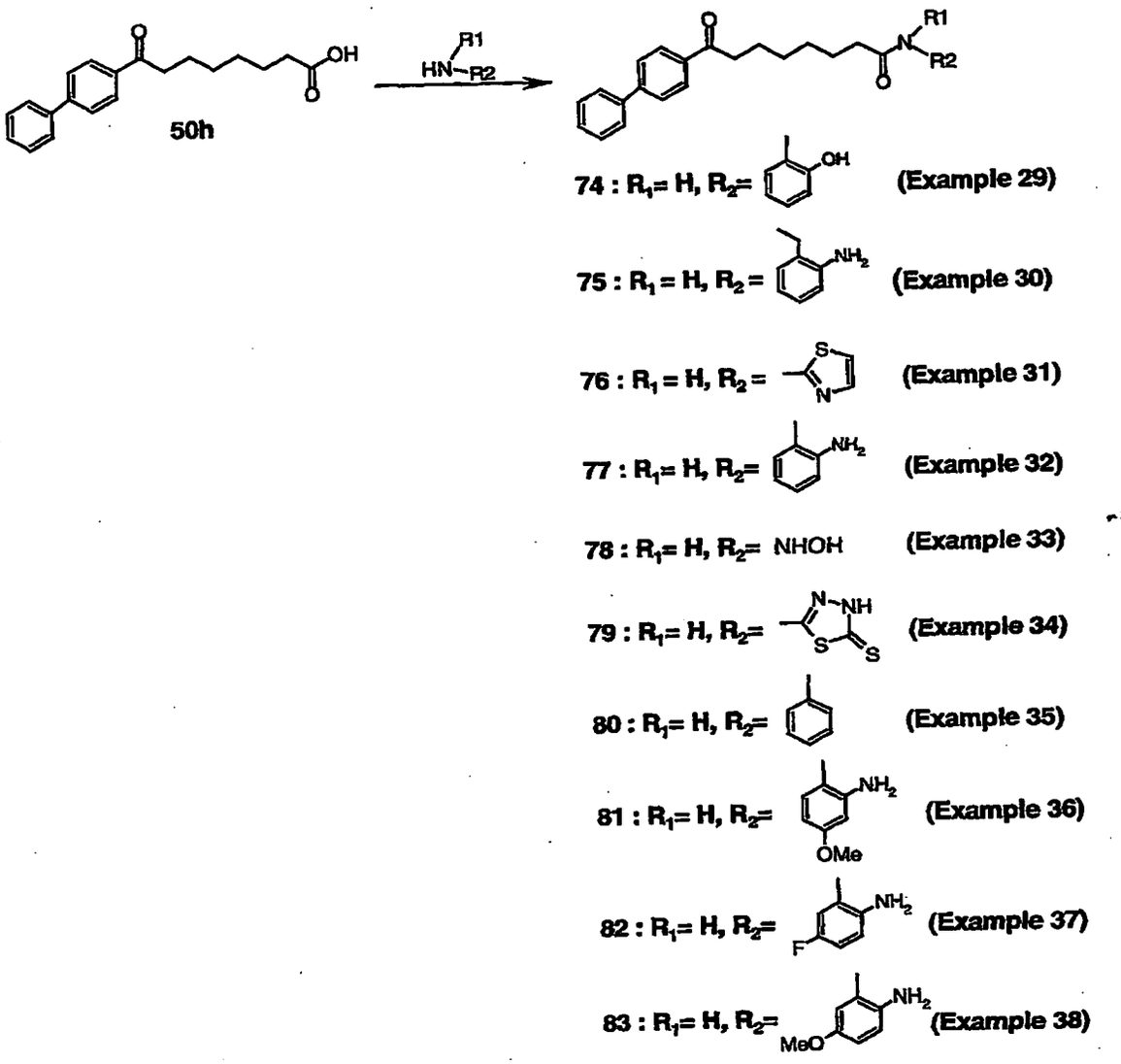
[0229] To a solution of 1-hydroxy-1-[(2-naphthyl)]-8-octanol **70** (715 mg, 2.63 mmol) in acetone (25 mL) was added manganese (IV) oxide (7.0 g, 81 mmol) and the reaction mixture was stirred at room temperature for 16 hours. The mixture was filtered through a short pad of Celite and the solvents were removed *in vacuo.* The title compound **71** (361 mg, 51%) was isolated by column chromatography (4:6 ethyl acetate:hexane). ^{1}H NMR (400 MHz, DNSO-d_6): δ 8.68 (s, 1H), 8.11 (d, 1H), 8.00 (m, 3H), 7.64 (m, 2H), 4.32 (t, 1H), 3.15 (t, J = 7.2 Hz, 2H), 1.67 (m, 2H), 1.40 (m, 2H), 1.32 (m, 8H).

Step 3: 1-Bromo-7-[(2-naphthoyl)]heptane (**72**):

[0230] To a solution of 7-(2-naphthoyl)-1-heptanol **71** (175 mg, 0.606 mmol) in ether (5mL) at 0˚C was added a solution of phosphorous tribromide (86 μL, 0.908 mmol) in ether (1 mL) dropwise and the reaction mixture was stirred at room temperature for 6 hours. Saturated sodium bicarbonate solution was added slowly and the mixture was extracted with ether (2 x 20 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvents were removed *in vacuo* to give the title compound **72** (141 mg, 70%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (s, 1H), 8.12 (m, 1H), 7.99 (m, 3H), 7.62 (m, 2H), 3.50 (t, 2H), 3.11 (t, 2H), 1.65 (m, 2H), 1.55 (m, 2H), 1.31 (m, 6H).

Step 4: *N*-(2-Aminophenyl)-7-(2-naphthoyl)heptanamine (**73**)

[0231] To a solution of 1-bromo-7-[(2-naphthoyl)]heptane **72** (62 mg, 0.17 mmol) in toluene (2 mL) and DMF (1 mL) was added 1,2-phenylenediamine (60 mg, 0.56 mmol) and *N*,*N*-diisopropylethylamine (36 μL, 0.21 mmol) and the reaction mixture was stirred at room temperature for 2 hours then at 75˚C for two hours and finally refluxed for 5 hours. Saturated sodium bicarbonate solution (5 mL) was added and the mixture was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with deionized water (20 mL), washed with brine (10 mL), and dried ($MgSO_4$). The solvents were removed *in vacuo* and the title compound **73** (2 mg, 3%) was isolated by column chromatography (3:7-4:6 ethyl acetate:hexane) followed by recrystallization from ether and hexane. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 8.00 (m, 3H), 7.64 (m, 2H), 6.52 (m, 1H), 6.47 (m, 1H), 638 (m, 2H), 4.46 (s, 2H), 4.30 (m, 1H), 3.17 (t, J = 7.4 Hz, 2H), 2.99 (m, 2H), 1.69 (m, 2H), 1.60 (m, 2H), 1.39 (m, 6H),



[0232] Example 35 is for illustration purpose only.

Example 29:

N-(2-Hydroxyphenyl)-7-[(4-biphenyl)carbonyl]heptanamide (74)

[0233] Following the procedure described in Example 22, but substituting carboxylic acid **50h** for carboxylic acid **50g** and 2-aminophenol for 1,2-phenylenediamine, the title compound **74** was obtained in 39% yield. ^{1}H NMR ($CDCl_3$:CD_3OD 5:1): δ 7.99 (d, J = 8.4 Hz, 2H), 7.60 (m, 4H), 7.41 (m, 4H), 7.02 (m, 1H), 6.91 (m, 1H), 6.81 (m, 1H), 2.98 (m, 2H), 2.41 (t, J = 7.5 Hz, 2H), 1.74 (m, 4H), 1.42 (m, 4H).

Example 30:

***N*-(2-Aminobenzyl)-7-[(4-biphenyl)carbonyl]heptanamide (75)**

[0234] Following the procedure described in Example 22, but substituting carboxylic acid **50h** for carboxylic acid **50g** and 2-aminobenzylamine for 1,2-phenylenediamine respectively, the title compound **75** was obtained in 32% yield. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.02 (d, J = 8.4 Hz, 2H), 7.71-7.61 (m, 4H), 7.37-7.51 (m, 3H), 7.12-7.01 (m, 2H), 6.70-6.62 (m, 2H), 5.76 (br s, 1H), 4.38 (d, J = 6.3 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H), 2.19 (t, J = 7.5 Hz, 2H), 1.80-1.58 (m, 4H), 1.45-1.32 (m, 4H).

Example 31:

***N*-(2-Thiazolyl)-7-[(4-biphenyl)carbonyl]heptanamide (76)**

[0235] Following the procedure described in Example 22, but substituting carboxylic acid **50h** for carboxylic acid **50g** and 2-aminothiazole for 1,2-phenylenediamine respectively, the title compound **76** was obtained in 11% yield. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.03 (d, J = 8.4 Hz, 2H), 7.6-7.7 (m, 4H), 7.39-7.53 (m, 4H), 7.07 (d, J = 4.2 Hz, 2H), 3.05 (t, J = 7.5 Hz, 2 H), 2.67 (t, J = 7.5 Hz, 2H), 1.72-1.82 (m, 4H),1.42-1.50 (m, 4H).

Example 32:

***N*-(2-Aminophenyl)-7-[(4-biphenyl)carbonyl]heptanamide (77)**

[0236] Following the procedure described in Example **22**, but substituting carboxylic acid 50h for carboxylic acid **50g**, the title compound **77** was obtained in 31% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, J = 8.4 Hz, 2H), 7.68 (d, 8.4 Hz, 2H), 7.62 (m, 2H), 7.51-7.35 (m, 3H), 7.16 (m, 1H), 7.04 (m, 1H), 7.75-6.80 (m, 2H), 3.83 (br s, 2H), 3.00 (t, J = 7.5 Hz, 2H), 2.39 (t, J = 7.2 Hz, 2H), 1.78 (m, 4H), 1.45 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$)
δ 24.08, 25.55, 28.87, 28.94, 36.79, 38.41, 118.13, 119.43, 124.38, 125.20, 127.05, 127.19, 127.21, 128.16, 128.62, 128.91, 135.61, 139.85, 140.78, 145.60, 1 71.82,200.09.

Example 33:

***N*-Hydroxy-7-[(4-biphenyl)carbonyl]heptanamide (78)**

[0237] Following the procedure described in Example 14, step 3, but substituting carboxylic acid 50h for carboxylic acid 37,and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **78** was obtained in 22% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 8.03 (d, J = 7.8 Hz, 2H), 7.70 (d, J = 7.8 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.55-7.38 (m, 3H), 3.02 (t, J = 6.9 Hz, 2H), 2.12 (t, J = 7.2 Hz, 2H), 1.75 (m, 2H), 1.66 (m, 2H), 1.41 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$):
δ 23.96, 25.06, 28.61(2), 32.54, 38.29, 126.98, 127.02, 128.02, 128.47, 128.71, 135.26, 139.55, 145.66, 171.09, 200.92.

Example 34:

***N*-(4,5-Dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)-7-[(4-biphenyl)carbonyl]-heptanamide (79)**

[0238] Following the procedure described in Example 22, but substituting carboxylic acid 50h for carboxylic acid **50g** and 5-amino-1,3,4-thiadiazole-2-thiol for 1,2-phenylenediamine respectively, the title compound **79** was obtained in 34% yield. ^{1}H NMR (300MHz, 20% CD_3OD in $CDCl_3$): δ 7.91 (d, J = 8.4 Hz, 2H), 7.58(d, J = 8.4 Hz, 2H), 7.52 (m, 2H), 7.38-7.26 (m, 3H), 2.90 (t, J = 7.2 Hz, 2H), 2.30 (t, J = 7.2 Hz, 2H), 1.62 (m, 4H), 1.30 (m, 4H).

Example 35:

***N*-Phenyl-7-[(4-biphenyl)carbonyl]heptanamide (80)**

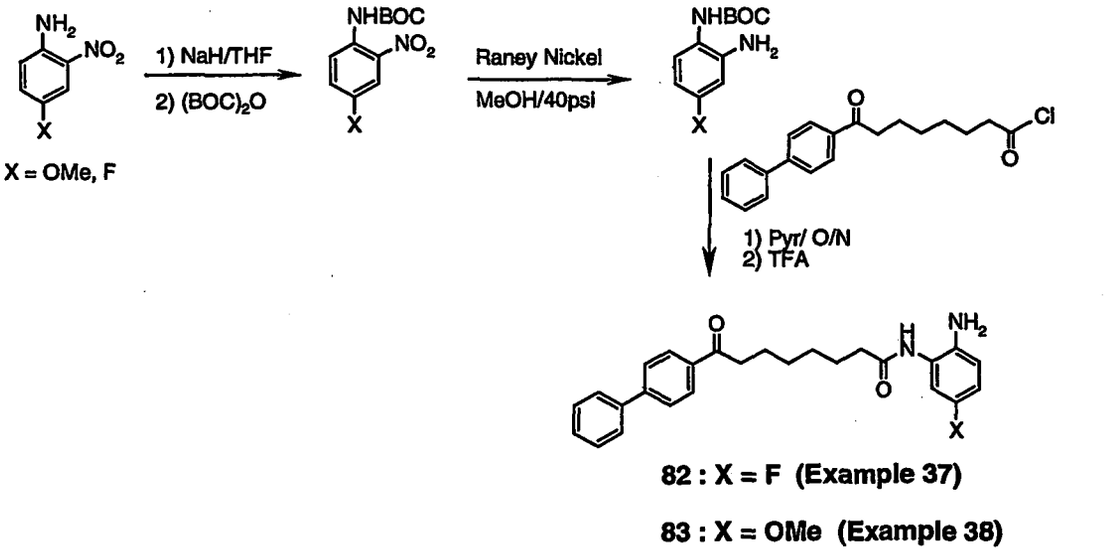
[0239] To a solution of carboxylic acid **50h** (310 mg, 1 mmol) in dichloromethane (5 mL) stirred at room temperature under nitrogen was added triethylamine (135μ L, 1 mmol), followed by BOP (442 mg, 1 mmol), aniline (108 μL, 1 mmol) and triethylamine (405 μL, 3 mmol). The resulting reaction mixture was stirred for **12** hours at room temperature. The solvent was removed and the mixture was quenched with water (5 mL), extracted with ethyl acetate (3 x 10 mL), dried ($MgSO_4$), concentrated. Purification by flash silica gel chromatography (5% methanol in dichloromethane) followed by crystallization from acetone afforded the corresponding amide **80** (20% yield). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 4H), 7.40-7.60 (m, 10H), 3.00 (m, 2H), 2.60 (m, 2H), 1.60 (m, 4H), 1.20 (m, 4H).

Example 36:

***N*-(4-(3-Amino)anisole)-7-[(4-biphenyl)carbonyl]heptanamide (81)**

[0240] Following the procedure described in Example 1, step **4**, but substituting 4-biphenyl carboxylic acid for **5**, the resulting carboxylic acid was substituted for **16** in Example 6. Then, to a solution of nitroamide (1 mmol) in THF/NH_4Cl

was added iron (1 mmol) and the mixture was stirred at room temperature for 4 hours. After filtration over Celite, water was added and the mixture was extracted from ethyl acetate to give a residue which was flashed over silica gel to give the title compound **81** obtained in 30% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 4H), 7.60-7.40 (m, 8H), 4.00 (s, 3H), 3.00 (m, 2H), 2.60 (m, 2H), 1.60 (m, 4H), 1.20 (m, 4H).



X = OMe, F

82 : X = F (Example 37)

83 : X = OMe (Example 38)

Example 37:

***N*-[(2-Amino-5-fluoro-phenyl]-7-[(4-biphenyl)carbonyl]heptanamide (82)**

Step 1: *N-tert*-Butyloxycarbonyl-3-fluoro-2-nitro aniline

[0241] To a solution of 3-fluoro-2-nitro aniline (1 g, 6.4 mmol) in anhydrous THF (20 mL) was added dropwise at 0˚C a solution of sodium hydride (510 mg, 12.8 mmol) in THF (10 mL). After 15 minutes, di-*tert*-butyl dicarbonate (2.8 g, 13 mmol) was added dropwise and the mixture was refluxed overnight. Water was added and the mixture was extracted with ethyl acetate. The residue was flashed on silica gel to give the desired product in 93% yield. MS (ESI) = 257 (MH^+)

Step 2: *N-tert*-Butyloxycarbonyl-3-fluoro-2-amino aniline

[0242] To a solution of the *N-tert*-Butyloxycarbonyl-3-fluoro-2-nitro aniline (950 mg, 2.5 mmol) in MeOH was added catalytic amount of Raney Nickel in water, hydrogen was applied at 40 psi and the mixture was stirred overnight. The mixture was filtered over Celite and the solvent was evaporated to give the desired product in 66% yield (550 mg). MS (ESI) = 226 (MH^+)

Step 3: *N*-[(2-Amino-5-fluoro-phenyl]-7-(4-biphenyl)carbonyl]heptanamide (82)

[0243] Following the procedure described in Example 1, step 4, but substituting 50h for 5, followed by Example 4, but substituting *N-tert*-butyloxycarbonyl-3-fluoro-2-amino aniline for 1,2-phenylenediamine, the title compound **82** was obtained in 27% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 4H), 7.60-7.40 (m, 8H), 3.00 (m, 2H), 2.60 (m, 2H), 1.60 (m, 4H), 1.20 (m, 4H).

Example 38:

***N*-(3-(4-Antino)anisole)-7-[(4-biphenyl)carbonyl]heptanamide (83)**

Step 1: *N-tert*-Butyloxycarbonyl-3-methoxy-2-nitro aniline

[0244] To a solution of 3-methoxy-2-nitro aniline (6.5 mmol) in anhydrous THF (20 mL) was added dropwise at 0˚C

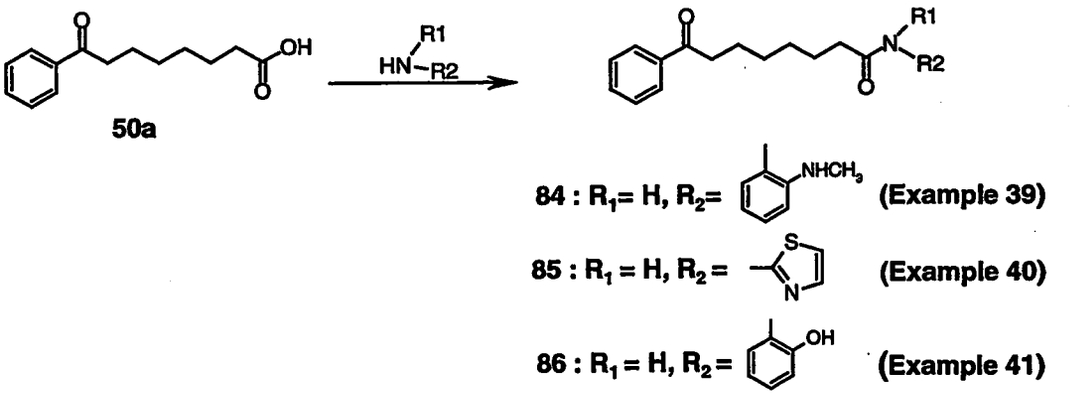
a solution of sodium hydride (13 mmol) in THF (10 mL). After 15 minutes, di-*tert*-butyl dicarbonate (13 mmol) was added dropwise and the mixture was refluxed overnight. Water was added and the mixture was extracted with ethyl acetate. The residue was flashed on silica gel to give the desired product in 95% yield. MS (ESI) = 269 (MH^+).

Step 2: *N-tert*-Butyloxycarbonyl-3-methoxy-2-amino aniline

[0245] To a solution of the *N-tert*-Butyloxycarbonyl-3-methoxy-2-nitro aniline (4 mmol) in MeOH was added catalytic amount of Raney Nickel in water, hydrogen was applied at 40 psi and the mixture was stirred overnight. The mixture was filtered over Celite and the solvent was evaporated to give the desired product in 55% yield. MS (ESI) = 239 (MH^+)

Step 3 : *N*-(3-(4-Amino)anisole)-7-[(4-biphenyl)carbonyl]heptanamide (**83**)

[0246] Following the procedure described in Example 1, step 4, but substituting **50h** for 5, followed by Example 4, step 1, 2, but substituting *N-tert*-butyloxycarbonyl-3-methoxy-2-amino aniline for 1,2-phenylenediamine, the title compound **83** was obtained in 32% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 4H), 7.60-7.40 (m, 8H), 4.00 (s, 3H), 3.00 (m, 2H), 2.60 (m, 2H), 1.60 (m, 4H), 1.20 (m, 4H).



Example 39:

***N*-(2-*N*-Methylaminophenyl)-7-(benzoyl)heptanamide (84)**

[0247] Following the procedure described in Example 35, but substituting **50h** for **80**, and *N*-methyl-1,2-phenylenediamine for aniline respectively, the title compound **84** was obtained in 27% yield. ^{1}H NMR (300MHz, $CDCl_3$): δ7.98-7.92

[0248] (m, 2H), 7.59-7.52 (m, 1H), 7.41-7.50 (m, 2H), 7.24-7.13 (m, 2H), 7.05-6.98 (br s, 1H), 6.77 (d, J = 7.8 Hz, 1H), 4.0 (br s, 1H), 2.99 (t, J = 7.4 Hz, 2H), 2.84 (s, 3H), 2.41 (t, J = 7.4 Hz, 2H), 1.85-1.70 (m, 4H), 1.48-1.35 (m, 4H).

Example 40:

***N*-(2-Thiazolyl)-7-(benzoyl)heptanamide (85)**

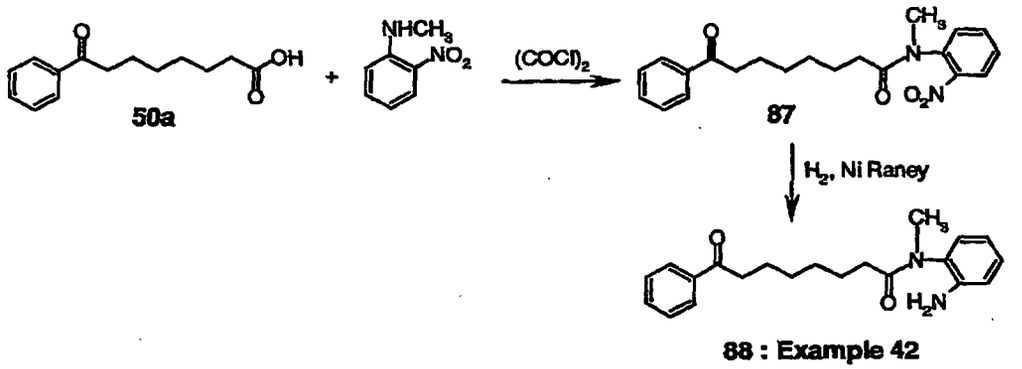
[0249] Following the procedure described in Example 35, but substituting respectively benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate for the BOP reagent and 2-aminothiazole for aniline, the title compound **85** was obtained in 54% yield. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.96 (d, J = 7.9 Hz, 2H), 7.60-7.54 (m, 1H), 7.42-7.50 (m, 3H), 7.0 (d, J = 3.7 Hz, 1H), 297 (t, J = 7.3 Hz, 2H), 257 (t, J = 7.4 Hz, 2H), 1.87-1.72 (m, 4H), 1.50-1.38 (m, 4H).

Example 41:

***N*-(2-Hydroxyphenyl)-7-(benzoyl)heptanamide (86)**

[0250] Following the procedure described in Example 40, but substituting the 1,2-aminophenol for the 2-aminothiazole, the title compound **86** was obtained in 36% yield.
^{1}H NMR (400MHz, $CDCl_3$): δ 8.01 (br s, 1H), 7.97-7.93 (m, 2H), 7.59-7.42 (2 m, 3H), 7.13-7.07 (m, 2H), 7.02-6.98 (m,

1H), 6.87-6.81 (m, 1H), 2.98 (t, J = 7.2 Hz, 2H), 2.45 (t, J = 7.2 Hz, 2H), 1.81-1.68 (m, 4H), 1.45-1.38 (m, 4H).



88 : Example 42

[0251] Example 42 is for illustration purpose only.

Example 42:

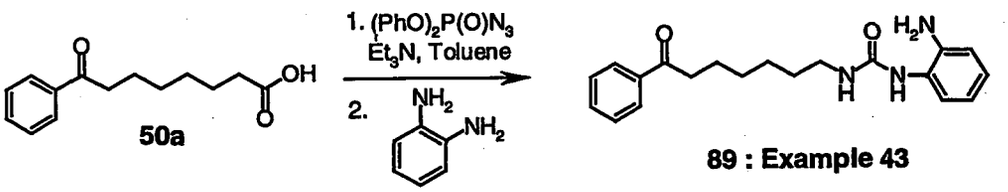
***N*-Methyl-*N*-(2-aminophenyl)-7-(benzoyl)heptanamide (88)**

Step 1: *N*-Methyl-*N*-(2-nitrophenyl)-7-(benzoyl)heptanamide (**87**)

[0252] To a solution of carboxylic acid **50a** (1 g, 4.27 mmol) in dichloromethane (5mL) was added DMF (100 μL) and oxalyl chloride (447 μL, 4.7 mmol). The mixture was stirred at room temperature for 12 hours and then cooled at 0˚C. The *N*-methyl-2-nitroaniline (714 mg, 4.7 mmol) dissolved in pyridine (2 mL) was transferred over the mixture, and the mixture was stirred at 50˚C for 12 hours. The reaction was quenched by addition of 1N HCl and extracted with dichloromethane. The organic layer was washed with a saturated solution of sodium bicarbonate, dried ($MgSO_4$), and concentrated. Purification by flash silica gel chromatography (2% methanol in dichloromethane) afforded the corresponding amide **87** (963 mg, 62% yield). MS (ESI) = 369 (MH^+).

Step 2: *N*-Methyl-*N*-(2-aminophenyl)-7-(benzoyl)heptanamide (**88**)

[0253] To a solution of amide **87** (420 mg, 1.14 mmol) in a mixture of ethyl acetate and methanol (5 mL, 9:1) was added catalytic amount of a suspension of Raney Nickel. The mixture was stirred at room temperature under hydrogen pressure for 2 hours and then without pressure for 10 hours. The reaction mixture was filtered through a short pad of Celite and the solvents were removed *in vacuo*. Purification by flash silica gel chromatography (2% methanol in dichloromethane) afforded the corresponding amide **88** (180 mg, 47% yield). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.96-7.90 (m, 2H), 7.58-7.41 (2 m, 4H), 7.17-7.10 (m, 1H), 6.98 (dd, J =1.5, 7.5 Hz, 1H), 6.80-672 (m, 2H), 3.18 (s, 3H), 2.91 (t, J = 7.2 Hz, 2H), 2.15-1.95 (m, 2H),1.73-1.51 (m, 4H), 1.35-1.20 (m, 4H).



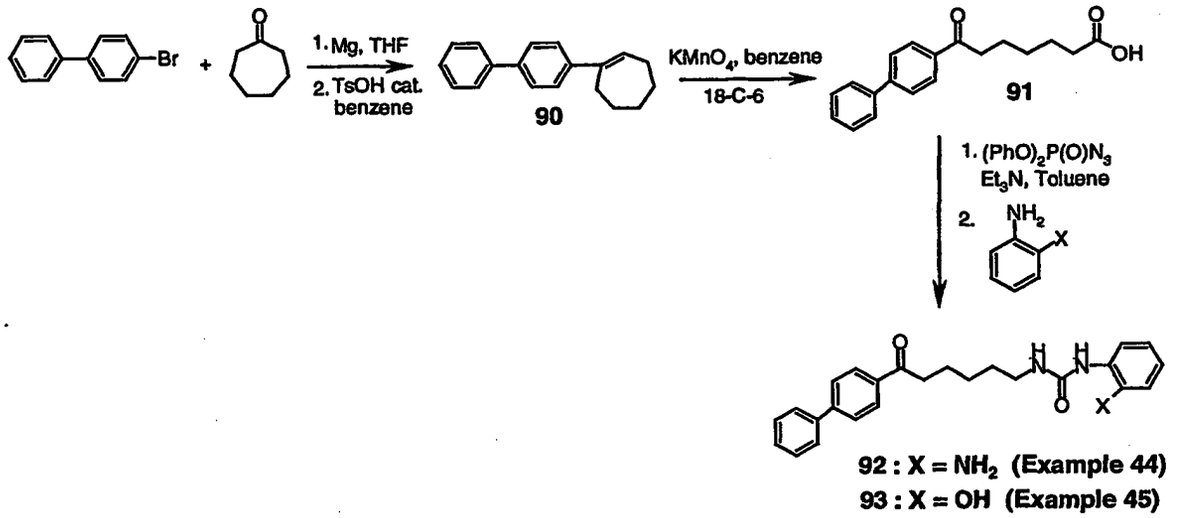
89 : Example 43

Example 43:

***N*-(2-Aminophenyl)-N'-[6-(benzoyl)hexyl]urea (89)**

[0254] To a stirred solution of carboxylic acid **50a** (500 mg, 2.13 mmol) in toluene (1.5 mL) at room temperature under nitrogen was added triethylamine (295 μL, 2.13 mmol), followed by diphenylphosphoryl azide (461 μL, 2.13 mmol). The reaction mixture was heated at 80˚C for 5 hours and 1,2-phenylenediamine (253 mg, 2.34 mmol) dissolved in 1 mL of

toluene was added. The reaction was stirred at 80°C for 12 hours. The mixture was quenched with water (5 mL), extracted with ethyl acetate (3 × 10 mL), dried ($MgSO_4$), and concentrated. Purification by flash silica gel chromatography (5% methanol in dichloromethane) followed by recrystallization from ethyl acetate and hexane afforded the corresponding urea 89 (340 mg, 47% yield) as a brown powder. ^1H NMR: (400MHz, $CDCl_3$) δ 7.95 (d, 2H, J = 7.2 Hz), 7.60-7.53 (m, 1H), 7.5-7.4 (m, 2H), 7.12-7.03 (m, 2H), 6.82-6.73 (m, 2H), 6.38 (br s, 1H), 4.92 (br s, 1H), 3.9 (br s, 2H), 3.23-3.12 (m, 2H), 2.95 (t, 2H, J = 7.3 Hz), 1.80-1.60 (m, 2H), 1.55-1.25 (2m, 6H).



Example 44:

***N*-(2-Aminophenyl)-N'-[5-((4-biphenyl)carbonyl)pentyl]urea (92)**

Step 1:1-Phenylcycloheptene (**90**)

i) *Grignard Reaction*

[0255] A dry two neck round bottom flask fitted with a condenser, a drying tube and an addition funnel was charged with magnesium turnings (517 mg, 21.5 mmol). Around 10% of the 4-bromobiphenyl (5 g, 21.5 mmol) dissolved in anhydrous THF (15 mL) was added via the addition funnel. When the reflux was maintained, the balance of halide was dropwise added and the mixture was refluxed for 2 hours. After being cooled to room temperature, the heptanone (2.5 mL, 21.2 mmol) dissolved in dry THF (10 mL) was dropwise added, and the mixture was stirred for 10 hours at room temperature. The reaction was quenched with 2N HCl (5 mL), extracted with diethyl ether (3 x 30 mL), dried ($MgSO_4$), and concentrated. Purification by flash silica gel chromatography (10% ethyl acetate in hexane) afforded the corresponding alcohol (4 g, 70% yield).

ii) Dehydration

[0256] In a round bottom flask fitted with a Dean Stark and a condenser was added a solution of alcohol (obtained above) in benzene (90 mL) and a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was refluxed for 3 hours and then cooled to room temperature. The mixture was washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), and concentrated to afford the corresponding alkene **90** (3.1 g, 84% yield). ^1H NMR (400MHz, $CDCl_3$: δ 7.70-7.35 (m, 9H), 6.15 (t, J = 8.0 Hz, 1H), 2.75-2.68 (m, 2H), 2.43-2.35 (m, 2H), 1.80-1.60 (m, 6H).

Step 2: 6-[(4-Biphenyl)carbonyl]hexanoic acid (**91**)

[0257] To a solution of cyclic alkene **90** (1.5 g, 6 mmol) dissolved in benzene (200 mL) was added 18-crown-6 (111 mg, 0.42 mmol) and $KMnO_4$ (2.37 g, 15 mmol). The reaction mixture was stirred at room temperature for 10 hours, and then quenched by addition of an aqueous solution of $NaHSO_3$ (100 mL) followed by 6N HCl until decoloration. The organic layer was extracted and washed with 0.5 N NaOH until a white precipitate was formed. The extracted aqueous layer was acidified with 6N HCl and then extracted with dichloromethane (5 x 200 mL). The combined organic layers

were dried ($MgSO_4$) and concentrated affording the corresponding acid **91** (480 mg, 27% yield) as a white solid. MS (ESI) = 311 (MH^+).

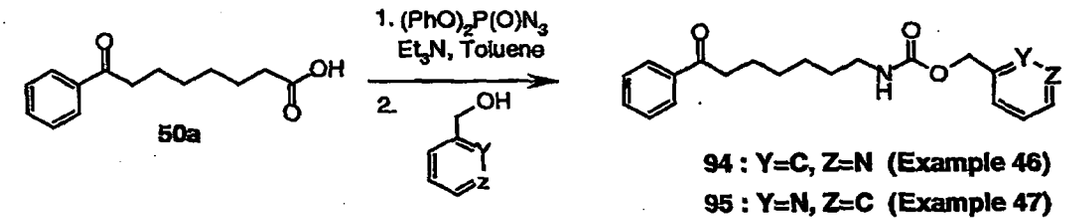
Step 3: *N*-(2-Aminophenyl)-N'-[5-((4-biphenyl)carbonyl)pentyl]urea (92)

[0258] Following the procedure described in Example **43**, but substituting carboxylic acid **91** for carboxylic acid **50a**, and substituting 1,2-phenylenediamine for 2-aminophenol the title compound **92** was obtained in 28% yield. ^1H NMR (400MHz, $CDCl_3$): δ 8.0 (d, J = 8.2 Hz, 2H), 7.70-7.60 (m, 5H), 7.52-7.38 (m, 4H), 7.20-7.00 (m, 3H), 6.93 (t, 1H), 5.73 (br s, 1H), 3.25-3.13 (m, 2H), 3.0 (t, 2H), 1.80-1.70 (m, 2H), 1.60-1.35 (m, 4H).

Example 45:

***N*-(2-Hydroxyphenyl)-N'-[5-((4-biphenyl)carbonyl)pentyl]urea (93)**

[0259] Following the procedure described in Example 43, but substituting carboxylic acid **91** for carboxylic acid **50a**, the title compound **93** was obtained in 22% yield. ^1H NMR (400MHz, $CDCl_3$): δ 8.03 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 7.1 Hz, 2H), 7.60-7.40 (m, 4H), 7.10-6.75 (3 m, 3H), 3.31 (t, J = 6.7 Hz, 2H), 3.04 (t, J = 6.9 Hz, 2H), 1.85-1.75 (m, 2H), 1.65-1.58 (m, 2H), 1.50-1.40 (m, 2H).



[0260] Example 46 and 47 are for illustration purpose only.

Example 46:

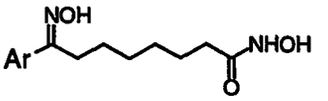
3-Pyridylmethyl-*N*-[6-(benzoyl)hexyl]carbamate (94)

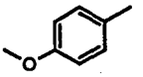
[0261] Following the procedure described in Example 43, but substituting 3-pyridylcarbinol for 2-aminophenol, the title compound **94** was obtained in 46% yield. ^1H NMR (400MHz, $CDCl_3$): δ 9.0 (s, 1H), 8.81 (d, J = 5.4 Hz, 1H), 8.35 (d, J = 8.4 Hz, 1H), 7.58-7.43 (m, 3H), 5.29 (s, 2H), 5.18 (br s, 1H), 3.23-3.16 (m 2H), 297 (t, J = 7.2 Hz, 2H), 1.80-1.68 (m, 2H), 1.60-1.47 (m, 2H), 1.47-1.3 (m, 4H).

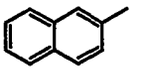
Example 47:

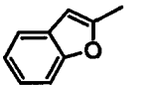
2-Pyridylmethyl-*N*-[6-(benzoyl)hexyl]carbamate (95)

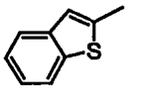
[0262] Following the procedure described in Example 43, but substituting the 2-pyridylcarbinol for 2-aminophenol, the title compound **95** was obtained in 35% yield. ^1H NMR (400MHz, $CDCl_3$): δ 9.0 (dd, J =7.2 Hz; 1.2 Hz, 1H), 8.3 (dt, J =7.2 Hz; 1.2 Hz, 1H), 7.97-7.92 (m, 2H), 7.81-7.75 (m, 2H), 7.58-7.42 (m, 3H), 5.75 (br s, 1H), 5.45 (s, 2H), 3.23-3.14 (m, 2H), 2.96 (t, J = 7.2 Hz, 2H), 1.78-1.68 (m, 2H), 1.58-1.48 (m, 2H), 1.42-1.34 (m, 4H).



96 : Ar =  **(Example 48)**

97 : Ar =  **(Example 49)**

98 : Ar =  **(Example 50)**

99 : Ar =  **(Example 51)**

Example 48:

***N*-Hydroxy-8-(E)-oximino-8-(4-methoxyphenyl)octanamide (E-96)**

[0263] Following the procedure described in Example 18, step 2, 3, but substituting 4-methoxybenzoyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **37** in Example 14, step 3, to afford the title compound **96** in 55% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.50 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 8.1 Hz, 2H), 3.81 (s, 3H), 2.75 (t, J = 7.2 Hz, 2H), 2.06 (m, 2H), 1.63-1.45 (m, 4H), 1.32 (m, 4H).

Example 49:

***N*-Hydroxy-8-(E)-oximino-8-(2-naphthyl)octanamide (97)**

[0264] Following the procedure described in Example 18, step 2, 3, but substituting 2-naphthoyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **37** in Example 14, step 3, to afford the title compound **97** in 40% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 8.00 (s, 1H), 7.90-7.40 (m, 6H), 2.91 (t, J = 7.2Hz, 2H), 2.07 (t, J = 6.9 Hz, 2H), 1.61 (m, 4H), 1.38 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$):
δ 25.03, 25.46, 25.86, 28.37, 28.92, 32.39, 123.43, 125.38, 125.90, 126.08, 127.15, 127.62, 127.94, 132.79, 133.I4, 133.17, 159.41, 171.17.

Example 50:

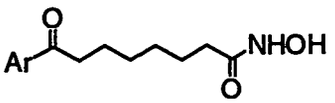
***N*-Hydroxy-8-(E)-oximino-8-(2-benzofuryl)octanamide (E-98) and *N*-Hydroxy-8(Z)-oximino-8-(2-benzofuryl)octanamide (Z-98)**

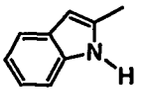
[0265] Following the procedure described in Example 1, step 4, but substituting 2-benzofurancarboxylic acid for 5, followed by Example 18, step 2, 3, but substituting 2-benzofurancarbonyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for 37 in Example 14, step 3, to afford the title compound **98** in 20% yield as a mixture of E and Z isomer in a ca 9 : 1 ratio. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (m, 2H), 7.22-7.00 (m, 3H), 2.82 (m, 2H), 2.00 (m, 2H), 1.62 (m, 4H), 1.22 (m, 4H).

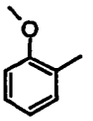
Example 51:

***N*-Hydroxy-8-(*Z*)-oximino-8-(2-benzo[b]thiophene)octanamide (99)**

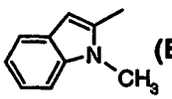
[0266] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **50m** for **37**, the title compound **99** was obtained in 30% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (m, 2H), 7.22-7.00 (m, 3H), 2.82 (m, 2H), 2.00 (m, 2H), 1.62 (m, 4H), 1.22 (m, 4H).

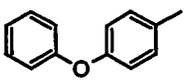


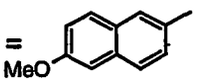
100 : Ar =  **(Example 52)**

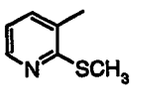
101 : Ar =  **(Example 53)**

102 : Ar =  **(Example 54)**

103 : Ar =  **(Example 55)**

104 : Ar =  **(Example 56)**

105a : Ar =  **(Example 57a)**

105b : Ar =  **(Example 57b)**

Example 52

***N*-Hydroxy-7-[2-(indolyl)carbonyl]heptanamide (100)**

[0267] Following the procedure described in Example 18, steps 2, 3, but substituting indole-2-carbonyl chloride for benzoyl chloride, and then substituting the resulting carboxylic acid for 37 in Example 14, step 3, and using 1.1 equivalent each of $NH_2OH{\cdot}HCl$ and triethylamine, the title compound **100** was obtained in 15% yield. ^1H NMR: (300 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.00-7.40 (m, 3H), 2.80 (m, 2H), 2.00-2.30 (m, 2H), 1.60 (m, 4H), 1.20 (m, 4H).

Example 53:

***N*-Hydroxy-7-(2-methoxybenzoyl)heptanamide (101)**

[0268] Following the procedure described in Example 18, step 2, 3, but substituting 2-methoxybenzoyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **37** in Example 14, step 3, using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, to afford the title compound **101** obtained in 33% yield. ^1H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.81 (dd, J = 8.1,1.8 Hz, 1H), 7.47 (m, 1H), 7.02-6.97 (m, 2H), 3.90 (s, 3H), 2.97 (t, J = 7.2 Hz, 2H), 2.10 (t, J = 7.2 Hz, 2H), 1.74-1.56 (m, 4H), 1.36 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$): δ 23.89, 25.05, 28.68, 28.60, 32.50, 43.28, 55.17, 111.35, 120.33, 128.03, 129.69, 133.26,158.18,171.18,204.09.

Example 54:

***N*-Hydroxy-7-[(cyclohexyl)carbonyl]heptanamide (102)**

[0269] Following the procedure described in Example 18, step 2, 3, but substituting 2-cyclohexylcarbonyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **37** in Example 14, step 3, using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, to afford the title compound 102 obtained in 38% yield. ^1H NMR (300 MHz,

$CDCl_3$): δ 2.45 (t, J = 6.9 Hz, 2H), 2.36 (m, 2H), 2.10 (m, 2H), 1.80-1.25 (m, 17H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$):
δ 23.13, 25.00, 25.35, 25.53, 28.22, 28.50, 28.51,32.47, 40.27, 50.61, 177.11, 215.62.

Example 55:

***N*-Hydroxy-7-[2-((*N*-methyl)indolyl)carbonyl]heptanamide (103)**

[0270] Following the procedure described in Example 1, step 4, but substituting 1-methyl indole-2-carboxylic acid for **5**, followed by Example 18, step 2, 3, but substituting *N*-methyl indole-2-carbonyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **37** in Example 14, step 3, using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, to afford the title compound 103 obtained in 30% yield. ^1H NMR: (300 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.00-7.20 (m, 3H), 2.90 (s, 3H), 2.80 (m, 2H), 2.00 (m, 2H), 1.60 (m, 4H), 1.20 (m, 4H).

Example 56:

***N*-Hydroxy-7-(4-phenoxybenzoyl)heptanamide (104)**

[0271] Following the procedure described in Example 1, step 4, but substituting 4-phenoxybenzoic acid for **5**, followed by Example 18, step 2, 3, but substituting 4-phenoxybenzoyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **37** in Example 14, step 3, using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, to afford the title compound **104** obtained in 44% yield. ^1H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.81 (d, J = 8.7 Hz, 2H), 7.23 (m, 2H), 7.08 (m, 1H), 6.94 (d, J = 8.1Hz, 2H), 6.87 (d, J = 8.1Hz, 2H), 2.81 (t, J = 7.2 Hz, 2H), 1.99 (m, 2H), 1.59 (m, 2H), 1.52 (m, 2H), 1.25 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$):
δ 24.00, 25.02, 28.56(2), 32.48, 37.96, 116.99, 119.89, 124.41, 129.79, 130.15, 131.15, 155.11, 161.83, 171.14, 199.86.

Example 57a:

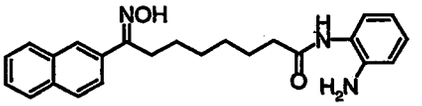
***N*-Hydroxy-7-[2-(6-methoxy)naphthoyl]heptanamide (105)**

[0272] Following the procedure described in Example 1, step 4, but substituting 2-(6-methoxy)naphthoic acid for **5**, followed by Example 18, step 2, 3, but substituting 2-(6-methoxy)naphthoyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **37** in Example 14, step 3, using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, to afford the title compound **105** obtained in 43% yield. ^1H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 8.39 (s, 1H), 7.98-7.16 (m, 5H), 7.56 (m, 1H), 3.95 (s, 3H), 3.06 (br t, J = 7.5Hz, 2H), 2.10 (m, 2H), 1.75 (m, 2H), 1.65 (m, 2H), 1.40 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$)
δ 24.09, 25.05, 28.59(2), 32.51, 38.07, 55.11, 105.49, 119.43, 124.19, 126.90, 127.57, 129. 48, 130.87, 131.88, 137.09, 159.53,171.20, 201.00.

Example 57b:

***N*-Hydroxy-7-[3-(2-thiomethyl)pyridyl)carbonyl]heptanamide (105b)**

[0273] Following the procedure described in Example 1, step 4, but substituting 3-(2-thiomethyl)pyridyl carboxylic acid for **5**, followed by Example 18, step 2, 3, but substituting 3-(2-thiomethyl)pyridyl carbonyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **37** in Example 14, step 3, using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, to afford the title compound **105** obtained in 39% yield. ^1H NMR (300MHz, 20% CD_3OD in $CDCl_3$): δ 8.58 (br d,J = 3.9 Hz, 1H), 8.74 (br d,J = 7.5 Hz, 1H), 7.50 (dd, J = 7.5, 4.8 Hz, 1H), 2.95 (t, J = 7.5 Hz, 2H), 2.51 (s, 3H), 2.12 (br t, 2H), 1.72 (m, 2H), 1.64 (m, 2H), 1.38 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$) δ 13.61, 23.64, 24.97, 28.42, 28.51, 32.44, 39.12, 117.71, 129.12, 137.29, 151.35, 161.62, 171.13, 200.67.

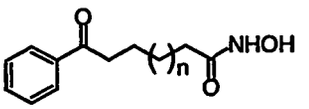


106 : Example 58

Example 58:

***N*-(2-Aminophenyl)-8-(E)-oximino-8-(2-naphthyl)octanamide (E-106) and *N*-(2-Aminophenyl)-8-(Z)-oximino-8-(2-naphthyl)octanamide (Z-106)**

[0274] Following the procedure described in Example 14, step 3, but substituting amide **63** for **37,** the title compound **106** was obtained in 30% yield (E/Z isomeric mixture, ca 5:1).^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.99 (s, 1H), 7.90-6.70 (m, 10H), 2.93 (t, J = 7.5Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 1.71 (m, 2H), 1.64 (m, 2H), 1.44 (m, 4H).



107 : n = 1 (Example 59)

108 : n = 2 (Example 60)

109 : n = 4 (Example 61)

Example 59:

***N*-Hydroxy-5-(benzoyl)pentanamide (107)**

[0275] Following the procedure described in Example 14, step 3, but substituting 5-benzoylpentanoic acid for **37** and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **107** was obtained in 52% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.86 (d, J = 6.9 Hz, 2H), 7.59-7.43 (m, 3H), 3.01 (br t, 2H), 2.18 (br t, 2H), 1.72 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$: δ 23.24, 24.78, 32.39, 37.79, 127.76, 128.36, 133.00, 136.38, 170.85, 200.82.

Example 60:

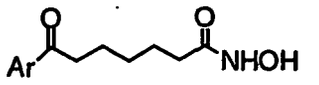
***N*-Hydroxy-6-(benzoyl)hexanamide (108)**

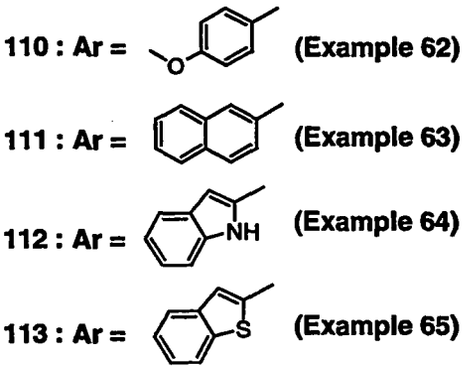
[0276] Following the procedure described in Example 14, step 3, but substituting 6-benzoylhexanoic acid for **37** and using 1.1 equivalent of $NH_2OH.HCl$and triethylamine each, the title compound **108** was obtained in 40% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.94 (d, J = 7:5Hz, 2H), 7.61-7.40 (m, 3H), 2.98 (t, J = 6.9 Hz, 2H), 2.15 (t, J = 6.6 Hz, 2H), 1.80-1.60 (m, 4H), 1.41 (m, 2H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$): 23.48, 25.04, 28.37, 32.39, 38.08, 127.87, 128.45, 133.03, 136.57, 171.16,201.05.

Example 61:

***N*-Hydroxy-8-(benzoyl)octanamide (109)**

[0277] Following the procedure described in Example 14, step 3, but substituting 8-benzoyloctanoic acid for **37** and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **109** was obtained in 46% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.86 (d, J = 7.5 Hz, 2H), 7.51-7.35 (m, 3H), 2.89 (t, J = 6.9 Hz, 2H), 2.02 (t, J = 6.6 Hz, 2H), 1.70-1.45 (m, 4H), 1.26 (m, 6H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$):
δ 23.95, 25.15, 28.59, 28.74, 28.78, 32.55, 38.27, 127.79,128.36, 132.91, 136.55, 171.27, 201.32.





Example 62:

***N*-Hydroxy-6-(4-methoxybenzoyl)hexanamide (110)**

[0278] Following the procedure described in Example 18, step 1, 2, 3, but substituting respectively ethyl-6-iodohexanoate for ethyl-7-iodoheptanoate and 4-methoxybenzoyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **37** in Example 14, step 3, using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, to afford the title compound **110** in 54% yield.^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_4$): δ 7.86 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H), 2.87 (t, J = 6.6 Hz, 2H), 2.07 (br t, 2H), 1.62 (m, 4H), 1.34 (m, 2H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$):
δ 23.68, 24.96, 28.32, 32.28, 37.63, 55.14, 113.49, 129.48, 130.13, 163.35, 171.06, 199.81

Example 63:

***N*-Hydroxy-6-(2-naphthoyl)hexanamide (111)**

[0279] Following the procedure described in Example 18, step 1, 2, 3, but substituting respectively ethyl-6-iodohexanoate for ethyl-7-iodoheptanoate and 2-naphthoyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **37** in Example **14,** step 3, using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, to afford the title compound **111** in 55% yield.^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 8.47 (s, 1H), 8.05-7.50 (m, 6H), 3.12, (br t, 2H), 2.15 (br t, 2H), 1.82-1.60 (m, 4H), 1.46 (m, 2H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$):
δ 23.59, 25.02, 28.36, 32.33, 38.06, 123.40, 126.56, 127.46, 128.21, 128.29, 129.29, 129.6 0, 132.25, 133.78, 135.37, 171.04, 201.04.

Example 64:

***N*-Hydroxy-6-[(2-indolyl)carbonyl]hexanamide (112)**

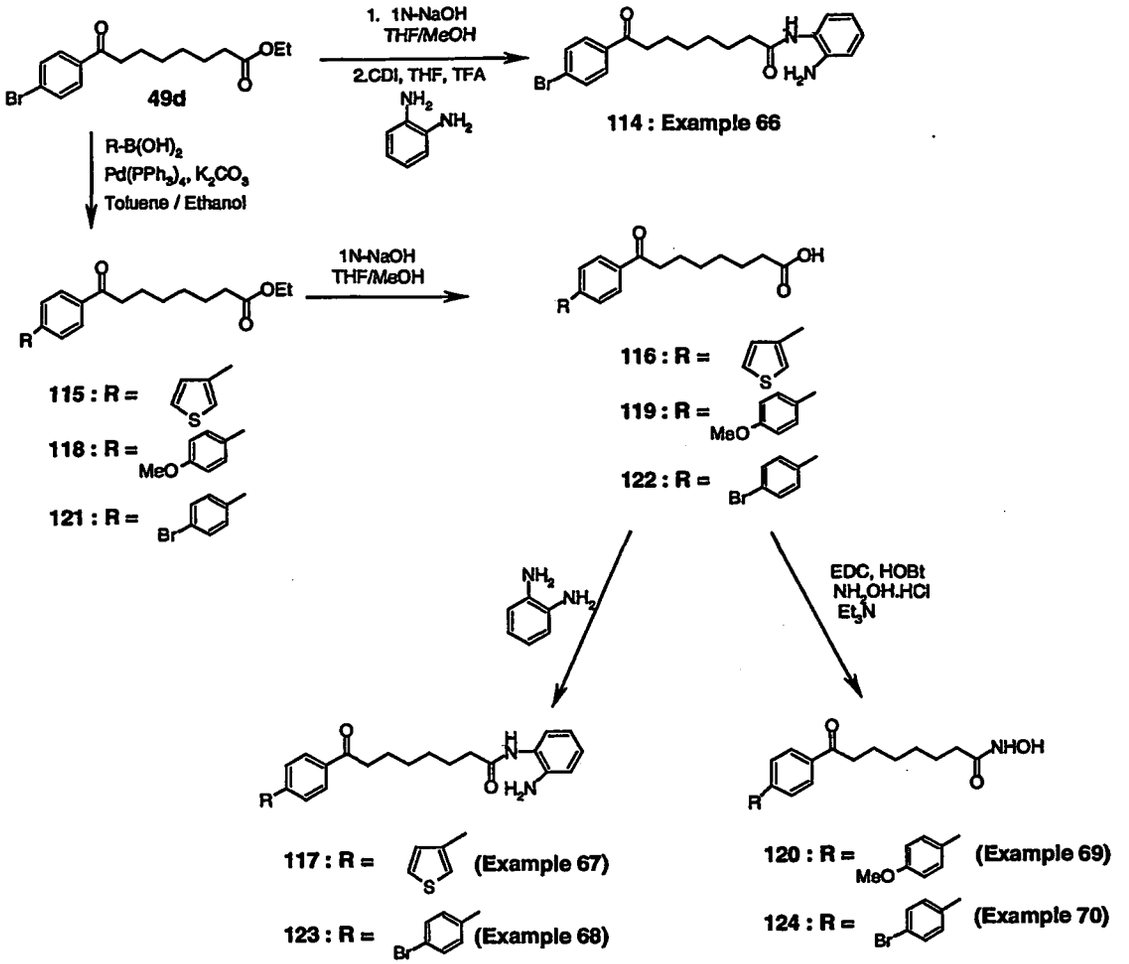
[0280] Following the procedure described in Example 1, step 4, but substituting indole-2-carboxylic acid for **5,** followed by Example 18, step 1, 2, 3, but substituting respectively ethyl-6-iodohexanoate for ethyl-7-iodoheptanoate and indole-2-carbonyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **37** in Example 14, step 3, using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, to afford the title compound **112** in 35% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.20-7.00 (m, 3H), 2.82 (m, 2H), 2.00 (m, 2H), 1.62 (m, 2H), 1.22 (m, 4H).

Example 65:

***N*-Hydroxy-6-[(2-benzo[b]thiophene)carbonyl]hexanamide (113)**

[0281] Following the procedure described in Example 18, step 1, 2, 3, but substituting respectively ethyl-6-iodohex-

anoate for ethyl-7-iodoheptanoate and 2-benzo[b]thiophene-carbonyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **37** in Example 14, step 3, using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, to afford the title compound **113** in 79%yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.20-7.00 (m, 3H), 2.80 (m, 2H), 2.00 (m, 2H), 1.60 (m, 2H), 1.20 (m, 4H).



Example 66:

***N*-(2-Aminophenyl)-7-(4-bromobenzoyl)heptanamide (114)**

[0282] Following the procedure described in Example 6, but substituting the carboxylic acid **50d** for the carboxylic acid **50g,** the title compound **114** was obtained in 30% yield.
^1H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.81 (d, J = 8.1Hz, 2H), 7.59 (d, J = 8.1Hz, 2H), 7.45 (br s, 1H), 7.16-6.73 (m, 3H), 2.92 (t, J = 7.2Hz, 2H), 2.36 (t, J = 7.2Hz, 2H), 1.73 (m, 4H), 1.41 (m, 4H). ^{13}C NMR (75MHz, 20% CD_3OD in $CDCl_3$): δ 23.85, 25.49, 28.79, 28.89, 36.68, 38.29, 118.07, 119.36, 124.29, 125.23, 127.06, 128.05, 129.53, 131.82, 135.60, 140.80, 171.86, 199.37.

Example 67:

***N*-(2-Aminophenyl)-7-[4-(3-thiophenyl)benzoyl]heptanamide (117)**

Step 1: Ethyl-7 [4-(3-thiophenyl)benzoyl]heptanoate (**115**)

[0283] To a mixture of 3-thiophene boronic acid (383 mg, 3 mmol) and bromoester **49d** (1.03 g, 3 mmol) were added anhydrous toluene (30 mL) and ethanol (1.5 mL) (20:1, c=1.0M) followed by 2M K_2CO_3 aqueous solution (3 mL, 6 mmol).

The reaction mixture was stirred under nitrogen for 30 minutes and then $Pd(PPh_3)_4$ (191 mg, 5mol%, 0.16 mmol) was quickly added. After 24 hours of reflux, the mixture was cooled to room temperature, filtered through a pad of Celite and rinsed with ethyl acetate (50mL). The organic solution was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Purification by flash silica gel chromatography (10% methanol in dichloromethane) followed by crystallization from ethyl acetate afforded the corresponding ester **115** (210 mg, 20% yield) as a white solid.

Step 2: 7-[4-(3-Thiophenyl)benzoyl]heptanoicacid (**116**)

[0284] Following the procedure described in Example 18, step 3, but substituting ester **115** for ester **49a,** the title compound **116** was obtained in 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$:CD_3OD 5:1): δ 7.87 (d, J = 8.2 Hz, 2H), 7:59 (d, J = 8.2 Hz, 2H), 7.50 (m, 1H), 7.34 (m, 2H), 2.88 (t, J = 7.7 Hz, 2H), 2.21 (m, 2H), 1.64(m, 2H), 1.53 (m, 2H), 1.30 (m, 4H).

Step 3: *N*-(2-Aminophenyl)-7-[4-(3-thiophenyl)benzoyl]heptanamide (**117**)

[0285] Following the procedure described in Example 22, but substituting carboxylic acid **116** for carboxylic acid **50g,** the title compound **117** was obtained in 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$:CD_3OD 5:1): 8 7.88 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 7.50 (m, 2H), 7.34 (m, 2H), 7.08 (m, 3H), 2.90 (m, 2H), 2.37 (t, J = 7.5 Hz, 2H), 1.65 (m, 4H), 1.35 (m, 4H).

Example 68:

***N*-(2-Aminophenyl)-7-[4-(4-bromophenyl)benzoyl]heptanamide hydrochloride (123)**

Step 1: Ethyl-7-[4-(4-bromophenyl)benzoyl]heptanoate **(121)**

[0286] Following the procedure described in Example 67, step 1, but substituting 4-bromophenyl boronic acid for 3-thiophene boronic acid, the title compound **121** was obtained in 52% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 8.02 (d, J = 8.7 Hz, 2H), 7.75-7.40 (m, 6H), 4.13 (q, J =6.9 Hz, 2H), 3.01 (t, J = 6.9 Hz, 2H), 2.32 (t, J = 7.2 Hz, 2H), 1.75 (m, 2H), 1.66 (m, 2H), 1.41 (m, 4H), 1.26 (t, J =6.9 Hz, 3H).

Step 2: 7-[4-(4-bromophenyl)benzoyl]heptanoic acid **(122)**

[0287] Following the procedure described in Example 18, step 3, but substituting ester **121** for ester **49a,** the title compound **122** was obtained in 88% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.91 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 7.50-7.37 (m, 4H), 2.89 (t, J = 7.2 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H),1.65 (m, 2H), 1.53 (m, 2H), 1.31 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in CD_3OD) δ 24.00, 24.50, 28.70(2), 33.77, 38.37,122.38,126.83,128.58(2), 131.85,135.64,138.53,144.27, 176.33, 200.65.

Step 3: *N*-2-Aminophenyl)-7-[4-(4-bromophenyl)benzoyl]heptanamide hydrochloride (**123**)

[0288] Following the procedure described in Example 6, but substituting the carboxylic acid **122** for the carboxylic acid **16,** the resulting amide was washed with 1N HCl and then precipitated out affording the title compound **123** in 67% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.97 (d, J = 8.7 Hz, 2H), 7.62-7.25 (m, 10H), 2.97 (t, J = 7.5 Hz, 2H), 2.49 (t, J = 7.5 Hz, 2H), 1.72 (m, 4H), 1.40 (m, 4H).

Example 69:

***N*-Hydroxy-7-[4-(4-methoxyphenyl)benzoyl]heptanamide (120)**

Step 1: Ethyl-7-[4-(4-methoxyphenyl)benzoyl]heptanoate (**118**)

[0289] Following the procedure described in Example 67, step 1, but substituting 2-methoxyphenyl boronic acid for 3-thiophene boronic acid, the title compound **118** was obtained in 26% yield.

Step 2: 7-[4-(4-methoxyphenyl)benzoyl]heptanoic acid (**119**)

[0290] Following the procedure described in Example 18, step 3, but substituting ester **118** for ester **49a,** the title compound **119** was obtained in 94% yield.^{1}H NMR ($CDCl_3$:CD_3OD 5:1): δ 7.88 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.6 Hz,

2H), 7.47 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 2.89 (d, J = 7.5 Hz, 2H), 3.50 (s, 3H), 2.19 (d, J = 7.5 Hz, 2H), 1.64 (m, 2H),1.55 (m, 2H),1.31 (m, 4H).

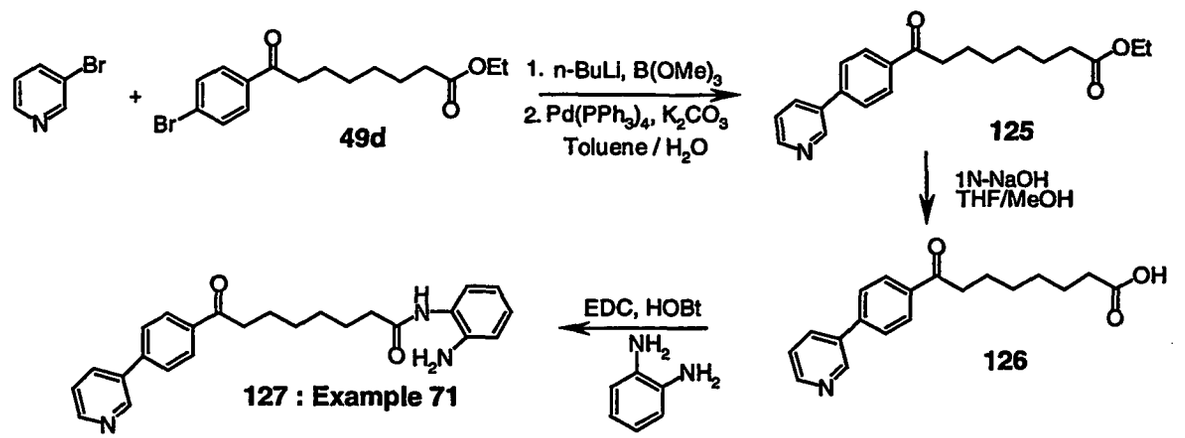
Step 3: *N*-Hydroxy-7-[4-(4-methoxyphenyl)benzoyl]heptanamide (**120**)

[0291] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **119** for **37,** and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **120** was obtained in 9% yield. MS (ESI) = 356 (MH^+).

Example 70:

***N*-Hydroxy-7-[4-(4-bromophenyl)benzoyl]heptanamide (124)**

[0292] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **122** for **37** and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **124** was obtained in 41%yield. ^1H NMR (300MHz, DMSO-*d6*): δ 10.33 (s, 1H), 8.66 (s,1H), 8.04-7.70 (m, 8H), 3.04 (m, 2H), 1.94 (m, 2H), 1.62 (m, 2H), 1.49 (m, 2H), 1.30 (m, 4H).



Example 71:

***N*-(2-Aminophenyl)-7-[4-(3-pyridyl)benzoyl]heptanamide (127)**

Step 1: Ethyl-7-[4-(3-pyridyl)benzoyl]heptanoate (**125**)

[0293] To a solution of 3-bromopyridine(728 mg, 4.6 mmol) in dry diethyl ether (9 mL) at -78˚C was added n-BuLi (2.5M solution in hexane, 1.8 mL, 4.5 mmol). The reaction mixture was stirred for 20 minutes at 0˚C. After a dropwise addition of trimethyl borate (0.5 mL, 4.5 mmol) the mixture was stirred for 1 hour at 0˚C and then a solution of bromoester **49d** (1.02 g, 3 mmol) in THF (9 mL) and water (2.3 mL) containing $Pd(PPh_3)_4$ (278mg, 8mol%, 0.27mmol) was added. The reaction mixture was refluxed at 70˚C for 24 hours, cooled to room temperature, filtered through a pad of Celite and rinsed with ethyl acetate. The solution was extracted with ethyl acetate (2 x 30 mL), washed with brine (10 mL), dried ($MgSO_4$) and concentrated. Purification by flash silica gel chromatography (1% methanol in dichloromethane) afforded the corresponding ester **125** (259 mg, 25% yield) as a white solid. MS (ESI) = 340 (MH^+).

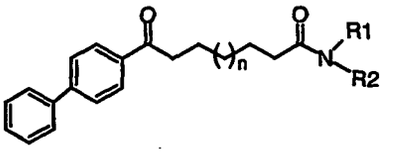
Step 2: 7[(3-pyridyl)-4-benzoyl]heptanoic acid (**126**)

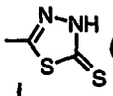
[0294] Following the procedure described in Example 18, step 3, but substituting ester **125** for ester **49a,** the title compound **126** was obtained in 75% yield.

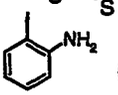
Step 3: *N*-(2-Aminophenyl)-7-[4-(3-pyridyl)benzoyl]heptanamide (**127**)

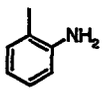
[0295] Following the procedure described in Example 22, but substituting carboxylic acid **126** for carboxylic acid **50g,**

the title compound **127** was obtained in 6% yield. ^{1}H NMR ($CDCl_3$:CD_3OD 5:1): δ 8.73 (d, J = 2.0 Hz, 1H), 8.48 (m, 1H), 7.96 (m, 3H), 7.59 (d, J = 8.6 Hz, 2H), 7.42 (m, 1H), 7.10 (m, 2H), 6.92 (m, 2H), 2.94 (t, J = 7.3 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.67 (m, 4H), 1.36 (m, 4H).



128 : n= 1, R_1= H, R_2=  **(Example 72)**

129 : n= 1, R_1= H, R_2=  **(Example 73)**

130 : n= 3, R_1= H, R_2=  **(Example 74)**

Example 72:

***N*-(4,5-Dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)-6-[(4-biphenyl)carbonyl]hexanamide (128)**

[0296] Following the procedure described in Example 18, step 1, 2, but substituting respectively ethyl-6-iodohexanoate for ethyl-7-iodoheptanoate and 4-bromobenzoyl chloride for benzoyl chloride, the resulting ester was substituted for **49d** in Example 67, step 1. Then, following the procedure described in Example 18, step 3, but substituting the final ester for ester **49a,** the resulting acid was substituted for **50g** in Example 22, to afford the title compound **128** in 33% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.97-(d, J = 8.7 Hz, 2H), 7.65-7.31 (m, 7H), 2.98 (t, J = 7.2Hz, 2H), 2.39 (t, J = 7.2Hz, 2H), 1.73 (m, 4H),1.40(m, 2H).

Example 73:

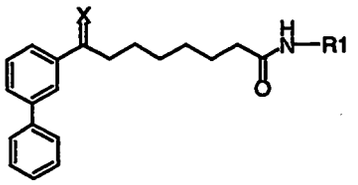
***N*-(2-Aminophenyl)-6-[(biphenyl)carbonyl]hexanamide (129)**

[0297] Following the procedure described in Example 18, step 1, 2, but substituting respectively ethyl-6-iodohexanoate for ethyl-7-iodoheptanoate and 4-bromobenzoyl chloride for benzoyl chloride, the resulting ester was substituted for **49d** in Example 67, step 1. Then, following the procedure described in Example 18, step 3, but substituting the final ester for ester **49a,** the resulting acid was substituted for **50g** in Example 22, to afford the title compound **129** in 29% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 8.01(d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.65-7.35 (m, 5H), 7.20-6.74 (m, 4H), 3.05 (t, J = 7.5 Hz, 2H, 2.44 (t, J = 7.5 Hz, 2H), 1.78 (m, 4H), 1.50 (m, 2H).

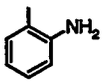
Example 74:

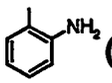
***N*-(2-Aminophenyl)-8-[(4-biphenyl)carbonyl]octanamide (130)**

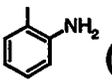
[0298] Following the procedure described in Example 18, step 1, 2, but substituting respectively ethyl-8-iodooctanoate for ethyl-7-iodoheptanoate and 4-bromobenzoyl chloride for benzoyl chloride, the resulting ester was substituted for **49d** in Example 67, step 1. Then, following the procedure described in Example 18, step 3, but substituting the final ester for ester **49a**, the resulting acid was substituted for **50g** in Example 22, to afford the title compound **130** in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 7.5 Hz, 2H), 7.55 (d, J = 7.5 Hz, 2H), 7.51-7.20 (m, 5H), 7.05-6.58 (m, 4H), 2.86 (t, J = 7.5 Hz, 2H), 2.24 (t, J = 7.5 Hz, 2H), 1.58-1.26 (m, 10H).

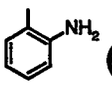


131 : X= O, R_1 = OH **(Example 75)**

132 : X= O, R_1 =  **(Example 76)**

133 : X= OH, R_1 =  **(Example 77)**

134 : X= NOH, R_1 =  **(Example 78)**

135 : X= $NOCH_3$, R_1 =  **(Example 79)**

Example 75:

***N*-Hydroxy-7-[(3-biphenyl)carbonyl]heptanamide (131)**

[0299] Following the procedure described in Example 18, step 1, 2, but substituting respectively 3-bromobenzoyl chloride for benzoyl chloride, the resulting ester was substituted for **49d** in Example 67, step 1. Then, following the procedure described in Example 18, step 3, but substituting the final ester for ester **49a,** the resulting acid was substituted in Example 14, step 3, using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, to afford the title compound **131** in 35%yield. ^1H NMR (300 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.88-7.30 (m, 8H), 2.96 (br t, 2H), 2.17 (m, 2H), 1.77-1.58 (m, 4H), 1.35 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ23.93, 25.12, 28.71(2), 32.73, 38.48, 126.61, 126.88, 127.08, 127.72, 128.85, 128.99, 131.58, 137.30, 140.06, 141.57, 171.82, 200.75.

Example 76:

***N*-(2-Aminophenyl)-7-[(3-biphenyl)carbonyl]heptanamide (132)**

[0300] Following the procedure described in Example 18, step 1, 2, but substituting respectively 3-bromobenzoyl chloride for benzoyl chloride, the resulting ester was substituted for **49d** in Example 67, step 1. Then, following the procedure described in Example 18, step 3, but substituting the final ester for ester **49a,** the resulting acid was substituted for 50g in Example 22, to afford the title compound **132** in 58% yield.^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (s, 1H), 8.08 (s, 1H), 7.88-7.30 (m, 8H), 7.20-6.62 (m, 4H), 2.99 (t, J = 7.2 Hz, 2H), 2.28 (t , J = 7.5 Hz, 2H), 1.77-1.58 (m, 4H), 1.36 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ23.85,25.39,28.71, 28.79, 36.30, 38.33, 117.49, 118.72, 124.00, 125.38, 126.38, 126.67, 126.74, 126.89, 127.56, 128.70, 128.84, 131.35, 137.21, 139.87, 140.90, 141.38, 172.14, 200.35.

Example 77:

***N*-(2-Aminophenyl)-8-(3-biphenyl)-8-hydroxy-octanamide (133)**

[0301] To a suspension of $NaBH_4$ (28.4mg, 0.75mmol) in THF (4mL) at -20˚C was added a solution of ketone **132** (300mg, 0.75mmol) in THF (1mL), followed by addition of methanol (1mL). After being stirred at 0˚C for 2 hours, the reaction was quenched by adding water (1mL). The solvent was removed under reduced pressure, and the resulting residue was then partitioned between ethyl acetate and water. After drying the combined organic phase ($MgSO_4$) and concentration, the crude was purified by flash chromatography using ethyl acetate as an eluent to give the title compound **133** (260mg, 86% yield). ^1H NMR (300MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.62-7.30 (m, 8H), 7.20-6.66 (m, 4H), 4.70 (br t,

1H), 2.35 (t, J = 7.2 Hz, 2H), 2.00-1.3 (m, 10H).

Example 78:

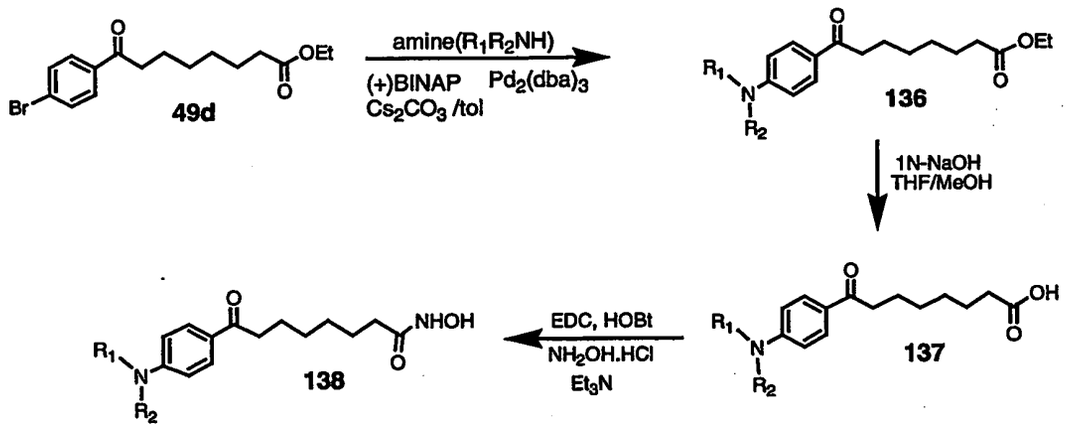
***N*-(2-Aminophenyl)-8-(*E*)-oximino-8-(3-biphenyl)octanamide (*E*-134)**

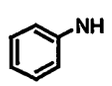
[0302] A mixture of **132** (100mg, 0.25mmol) and $H_2OH{\cdot}HCl$ (70mg, 1.0mmol) in pyridine (0.4mL) was heated at 50˚C for 16 hours. The pyridine was then removed under reduced pressure and the resulting residue was partitioned between ethyl acetate and water. After drying the combined organic phase ($MgSO_4$) and concentration, the crude was purified by flash chromatography using ethyl acetate as an eluent to give the title compound **134** (81mg, 78% yield) as a mixture of E and Z isomer in a ca 5:1 ratio. ^1H NMR for a major E isomer (300 MHz, $CDCl_3$): δ 9.25 (br s, 1H), 7.80 (m, 1H), 7.62-7.35 (m, 8H), 7.20-6.62 (m, 4H), 3.82 (br s, 2H), 2.85 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.68 (m, 2H), 1.59 (m, 2H),1.39 (m, 4H).

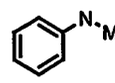
Example 79:

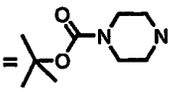
***N*-(2-Aminophenyl)-8-(*E*)-*O*-methyl-oximino-8-(3-biphenyl)octanamide (*E*-135)**

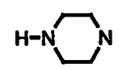
[0303] Following the procedure described in Example 78, but substituting *N*-methoxylamine · HCl for *N*-hydroxylamine · HCl, the title compound **135** was obtained in 57% yield as a mixture of E and Z isomer in a ca 3 : 1 ratio. ^1H NMR for a major E isomer (300 MHz, $CDCl_3$):
δ 7.84 (m, 1H), 7.62-7.31 (m, 8H), 7.22-6.75 (m, 4H), 3.99 (s, 3H), 3.80 (br s, 2H), 2.78 (t, J = 7.5 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.72 (m, 2H), 1.57 (m, 2H), 1.39 (m, 4H).

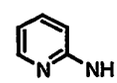


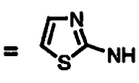
138a : R_1R_2N =  **(Example 80)**

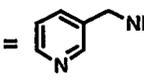
138b : R_1R_2N =  **(Example 81)**

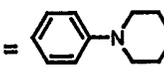
138c1 : R_1R_2N =  **(Example 82a)**

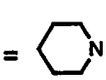
138c2 : R_1R_2N =  **(Example 82b)**

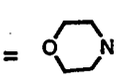
138d : R_1R_2N =  **(Example 83)**

138e : R_1R_2N =  **(Example 84)**

138f: R_1R_2N =  **(Example 85)**

138g : R_1R_2N =  **(Example 86)**

138 h : R_1R_2N =  **(Example 87)**

138 i : R_1R_2N =  **(Example 88)**

Example 80:

***N*-Hydroxy-7-[4-(*N*-phenyl)benzoyl]heptanamide (138a)**

Seep 1: Ethyl-7-[4-(*N*-phenyl)benzoyl]phentanoate (**136a**)

[0304] To a mixture of bromoester **49d** (171 mg, 0.5 mmol), $Pd_2(dba)_3$(9.2 mg, 0.01 mmol), BINAP (12.4 mg, 0.032 mmol), and Cs_2CO_3 (228 mg, 0.7 mmol) dissolved in dry toluene (2 mL), was added aniline (56 mg, 0.6 mmol). The reaction mixture was degassed for 10 minutes by bubbling with nitrogen stream and then heated at 100˚C until TLC showed no starting material **49d** (ca 20-30 hours). After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and water and then the combined organic layers were dried ($MgSO_4$), and concentrated. Purification by flash chromatography using ethyl acetate and hexane as eluents gave the title compound **136a** in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 9.0 Hz, 2H), 7.36-6.98 (m, 7M, 6.30 (s,1H), 4.11 (q, J = 7.2 Hz, 2H), 2.87 (t, J = 7.5 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H),1.72 (m, 2H), 1.63 (m, 2H), 1.37 (m, 4H), 1.25 (t, J = 7.2Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$)
δ 14.18, 24.53, 24.77, 28.92, 19.01, 34.24, 37.88, 60.12, 114.40, 120.48, 123.1, 128.65, 12 9.41, 130.26, 140.67, 148.20, 174.77, 198.63.

Step 2: 7-[4-(*N*-phenyl)benzoyl]heptanoic acid (**137a**)

[0305] Following the procedure described in Example 18, step 3, but substituting ester **136a** for ester **49a,** the title compound **137a** was obtained in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, J = 9.0 Hz, 2H), 7.36-7.17 (m, 4H), 7.05 (m, 1H), 7.00 (d, J = 9.0 Hz, H), 3.95 (br s, 1H), 2.88 (t, J = 7.5Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.72 -1.58 (m, 4H), 1.38 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$)
δ 24.56, 24.58, 28.77, 28.90, 33.82,
33.80, 114.14, 120.29, 122.87, 128.01, 129.27, 130.30, 140.63, 148.52, 176.68, 199.47.

Step 3: *N*-(Hydroxy)-7-[4-(*N*-phenyl)benzoyl]heptanamide **(138a)**

[0306] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **137a** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **138a** was obtained in 43% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.85 (d, J = 8.7 Hz, 2H), 7.36-7.00 (m, 7H), 2.89 (t, J = 7.2Hz, 2H), 2.10 (t, J = 7.5 Hz, 2H), 1.72 -1.58 (m, 4H), 1.37 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$)
δ 24.48, 25.03, 28.55, 28.62, 32.50, 37.62, 113.94, 120.22, 122.73,
127.54, 129.15, 130.28, 140.63, 148.86, 171.12, 199.83.

Example 81:

***N*-Hydroxy-7-[4-(*N*-methyl-*N*-phenyl)benzoyl]heptanamide (138b)**

Step 1: Ethyl-7-[4-*N*-methyl-*N*-phenyl)benzoyl]heptanoate (**136b**)

[0307] Following the procedure described in Example **80**, step 1, but substituting *N*-methylaniline for aniline, the title compound **136b** was obtained in 11% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 9.3 Hz, 2H), 7.39 (m, 2H), 7.21 (m, 3H), 6.74(d,J= 9.3 Hz, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.36 (s, 3H), 285 (t, J = 7.5 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 1.74-1.56 (m, 4H), 1.36 (m, 4H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.20, 24.63, 24.76, 28.92, 29.02, 34.23, 37.79, 40.11, 60.07, 113.50, 125.45, 125.94, 126.88, 129.75, 129.83, 147.23, 152.46, 173.70, 198.61.

Step 2: 7-[4-(-(*N*-methyl-*N*-phenyl)benzoyl]heptanoic acid (**137b**)

[0308] Following the procedure described in Example 18, step 3, but substituting ester **136b** for ester **49a,** the title compound **137b** was obtained in 95% yield. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.81 (d, J = 9.3 Hz, 2H), 7.40 (m, 2H), 7.21 (m, 3H), 6.75 (d, J = 9.3 Hz, 2H), 3.37 (s, 3H), 2.86 (t, J = 7.5 Hz, 2H), 2.34 (t, J = 7.5 Hz, 2H), 1.78-1.56 (m, 4H), 1.38 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.47, 24.67, 28.83, 28.98, 33.92, 37.79, 40.13, 113.48, 125.51, 125.99, 126.77, 129.77, 1.29.92, 147.21, 152.53, 179.51,198.92

Step 3: *N*-Hydroxy-7-[4-(*N*-methyl-*N*-phenyl)benzoyl]heptanamide (**138b**)

[0309] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **137b** for **37,** and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **138b** was obtained in 37% yield. ^1H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.74 (d, J = 9.0 Hz, 2H), 7.36 (m, 2H), 7.17 (m, 3H), 6.68 (d, J = 9.0 Hz, 2H), 3.31 (s, 3H), 2.80 (t, J = 7.2 Hz, 2H), 2.03 (t, J = 7.2 Hz, 2H), 1.70-1.50 (m, 4H), 1.30 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$) δ 24.53, 25.01, 28.53, 28.60, 32.47, 37.57, 38.87,113.10,125.55,125.96,126.03,129.62, 129.87,146.85,152.67,171.14,199.83.

Example 82a:

***N*-Hydroxy-7-[4-(1-(4-*tert*-butyloxycarbonylpiperazinyl))benzoyl]heptanamide (138c1)**

Step 1: Ethyl-7-[4-(1-(4-*tert*-butyloxycarbonylpiperazinyl))benzoyl]heptanoate (**136c1**)

[0310] Following the procedure described in Example **80**, step 1, but substituting 1-butyloxycarbonylpiperazine for aniline, the title compound **136c1** was obtained in 14% yield.^1H NMR (300MHz, $CDCl_3$): δ 7.88 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 4.12 (q, J = 7.2Hz, 2H), 3.58(m, 4H), 3.32(m, 4H), 287(t, J = 7.5Hz, 2H), 2.28(t, J = 7.5 Hz, 2H), 1.72 (m, 2H), 1.63 (m, 2H), 1.49 (s, 9H), 1.38 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.15, 24.48, 24.73, 28.31, 28.89, 28.97, 34.20, 37.85, 42.30, 47.30, 60.06, 80.03, 113.71, 127.74, 130.02, 153.77, 154.54, 173.68, 198.66.

Step 2: 7-[4-(1-(4-*tert*-butyloxycarbonylpiperizinyl))benzoyl]heptanoic acid (**137c1**)

[0311] Following the procedure described in Example 18, step 3, but substituting ester **136c1** for ester **49a,** the title compound **137c1** was obtained in 93% yield. ^1H NMR (300MHz, $CDCl_3$): δ 7.88 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 3.58 (m, 4H), 3.33 (m, 4H), 2.88 (t, J = 7.5 Hz, 2H), 2.34 (t, J = 7.5 Hz, 2H), 1.74-1.58 (m, 4H), 1.49 (s, 9H), 1.39 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$)
δ 24.47, 28.30(2), 28.79, 28.92,33.87,
37.81, 42.40, 47.24, 80.16, 113.69, 127.63, 130.06, 153.75, 154.61,179.01, 198.86.

Step 3: *N*-Hydroxy-7-[4-(1-(4-*tert*-butyloxycarbonylpiperazinyl))benzoyl]-heptanamide (**138c1**)

[0312] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **137c1** for 37, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **138c1** was obtained in 46% yield.^1H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.76 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 3.48 (m, 4H), 3.24 (m, 4H), 2.77 (t, J = 6.9 Hz, 2H), 1.98 (t, J = 7.2 Hz, 2H),1.70-1.48 (m, 4H), 1.37 (s, 9H),1.25 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$) δ 24.39, 25.03, 28.04, 28.56, 28.61, 32.50, 37.67, 42.93, 46.96, 80.35, 113.51, 127.11, 130 .07, 153.81, 154.73, 171.06, 198.87.

Example 82b:

***N*-Hydroxy-7-[4-(1-(piperazinyl))benzoyl]heptanamide (138c2)**

[0313] To a stirred solution of **138c1** (56 mg, 0.129 mmol) in dichloromethane(0.5 mL) at room temperature was added trifluoroacetic acid (0.2 mL, 2.6 mmol). After being stirred at room temperature for 30 minutes, the reaction mixture was concentrated under reduced pressure. The residue obtained was dissolved in water (2 mL), neutralized with saturated aqueous sodium bicarbonate solution (2 mL), extracted with ethyl acetate and then with 10% methanol in chloroform. The combined organic layers were dried and concentrated under reduced pressure to give the title compound **138c2** (20 mg, 46% yield).^1H NMR (300MHz, 20% CD_3OD in $CDCl_3$): δ 7.75 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 3.24 (m, 4H), 2.91 (m, 4H), 2.77(t, J = 7.2 Hz, 2H), 2.28 (t, J = 6.6 Hz, 2H), 1.58 (m, 4H),1.25 (m, 4H).

Example 83:

***N*-Hydroxy-7-[4-(*N*-2-ammopyridyl)benzoyl]heptanamide (138d)**

Step 1: Ethy-7-[4-(*N*-2-aminopyridyl)benzoyl]heptanoate (**136d**)

[0314] Following the procedure described in Example **80**, step 1, but substituting 2-aminopyridine for aniline, the title compound **136d** was obtained in 40% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (dd, J = 8.1,1.2 Hz,1H), 7.93 (d, J = 8.7 Hz, 2H), 7.57 (m,1H), 7.48 (d, J = 8.7 Hz, 2H), 7.17 (s,1H), 6.93 (m,1H), 6.84 (m,1H), 5.39 (t, J = 5.7 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.78-1.56 (m, 4H), 1.38 (m, 4H), 1.25 (t, J =7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.21, 24.43, 24.78, 28.94, 29.00, 34.26, 38.04, 60.15, 110.40, 116.32, 117.19; 129.86, 130.27, 137.77, 145.24, 148.23, 154.45, 173.78, 198.92.

Step 2: 7-[4-(*N*-2-aminopyridyl)benzoyl]heptanoic acid (**137d**)

[0315] Following the procedure described in Example 18, step 3, but substituting ester **136d** for ester **49a,** the title compound **137d** was obtained in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, J = 9.0 Hz, 2H), 7.36-7.17 (m, 4H), 7.05 (m, 1H), 7.00 (d, J = 9.0 Hz, 2H), 3.95 (br s, 1H), 2.88 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.72 -1.58 (m, 4H),1.38 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$)
δ 24.56, 24.58, 28.77, 28.90,33.82,
33.80, 114.14, 120.29, 122.87, 128.01, 129.27, 130.30, 140.63, 148.52, 176.68, 199.47.

Step 3: *N*-Hydroxy-7-[4-(*N*-2-aminopyridyl)benzoyl]heptanamide (**138d**)

[0316] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **137d** for **37,** and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **138d** was obtained in 11% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.61 (br s, 1H), 8.20 (m,1H), 7.95-6.80 (m, 6H), 2.88 (t, J = 7.5 Hz, 2H),1.91 (t, J = 7.5 Hz, 2H), 1.68-1.40 (m, 4H), 1.26 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) 24.27, 25.16, 28.59(2), 32.37, 37.41,111.96, 115.80, 116.62, 128.70, 129.54,137.81,146.344,147.43,155.16,169.43,198.48.

Example 84:

***N*-Hydroxy-7-[4-(*N*-2-aminothiazolyl)benzoyl]heptanamide (138e)**

Step 1: Ethyl-7-[4-(*N*-2-aminothiazolyl)benzoyl]heptanoate (**136e**)

[0317] Following the procedure described in Example **80**, step 1, but substituting 2-aminothiazole for aniline, the title compound **136e** was obtained in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.05 (br s, 1H), 7.97 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 3.6 Hz, 1H), 6.75 (d, J = 3.6 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 2.92 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.78-1.56 (m, 4H), 1.38 (m, 4H), 1.26 (t, J =7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.07, 24.24, 24.64, 28.79, 28.84, 34.12, 37.95, 60.08,108.66,115.90,129.90,130.35,138.23,144.74,163,98,173.75, 198.88.

Step 2: 7-[4-(*N*-2-aminothiazolyl)benzoyl]heptanoic acid (**137e**)

[0318] Following the procedure described in Example 18, step 3, but substituting ester **136e** for ester **49a**, the title compound **137e** was obtained in 98% yield. ^{1}H NMR (300MHz, 20% CD_3OD in $CDCl_3$): δ 7.44 (d, J = 9.0 Hz, 2H), 7.62 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 3.6 Hz, 1H), 6.83 (d, J =3.6 Hz, 1H), 2.96 (t, J = 7.5 Hz, 2H), 2.30 (t, 2H, 7.5 Hz, 2H), 1.73 (m, 2H), 1.64 (m, 2H), 1.41 (m, 4H).^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$):
δ 23.86, 24.02,28.21(2), 33.18, 37.23, 108.65, 115.35, 129.20(2), 137.81, 145.08, 163.90, 175.84, 199.74.

Step 3: *N*-Hydroxy-7-[4-(*N*-2-aminothiazolyl)benzoyl]heptanamide (**138e**)

[0319] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **137e** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **138e** was obtained in 28% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in CD_3OD): δ 7.88 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 3.3 Hz, 1H), 6.71 (d, J = 3.3 Hz, 1H), 2.87 (t, J = 6.9 Hz, 2H), 2.04 (t, J = 7.5 Hz, 2H), 1.72-1.50 (m, 4H), 1.31 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$) δ 24.24, 25.03, 28.58(2), 33.52, 37.83,108.94,115.92,129.83,138.21,145.08, 171.10,199.97.

Example 85:

***N*-Hydroxy-7-[4-(*N*-3-aminomethylpyridyl)benzoyl]heptanamide (138f)**

Step 1: Ethyl-7[4-(*N*-3-aminomethylpyridyl)benzoyl]heptanoate (**136f**)

[0320] Following the procedure described in Example **80**, step 1, but substituting 3-aminomethylpyridine for aniline, the title compound **136f** was obtained in 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (br s, 1H), 8.50 (d, J = 3.9 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 7.65 (m, 1H), 7.24 (dd, J = 7.5,1.5 Hz, 1H), 6.58 (d, J = 8.7 Hz, 2H), 5.39 (t, J = 5.7 Hz, 1H), 4.42 (d, J = 5.7 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 2.82 (t, J = 7.5 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 1.74-1.56 (m, 4H),1.35 (m, 4H), 1.24 (t, J =7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.01, 24.44, 24.58, 28.73, 28.83, 34.03,37.54, 44.69, 59.92, 111.47, 123.37, 126.53, 130.24, 133.90, 134.74, 148.51, 148.68, 151.46, 173.56,198.44.

Step 2: 7-[4-(*N*-3-aminomethylpyridyl)benzoyl]heptanoic acid (**137f**)

[0321] Following the procedure described in Example 18, step 3, but substituting ester **136f** for ester **49a**, the title compound **137f** was obtained in 83% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 8.52 (br s,1H), 8.54 (d, J = 3.9 Hz, 1H), 7.79 (d, J = 9.0 Hz, 2H), 7.70-7.24 (m, 3H), 6.59 (d, J = 9.0 Hz, 2H), 4.40 (s, 2H), 2.84 (t, J = 7.5 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 1.74-1.54 (m, 2H), 1.37 (m, 4H).

Step 3: *N*-Hydroxy-7-[4-(*N*-3-aminomethylpyridyl)benzoyl]heptanamide (**138f**)

[0322] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **137f** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **138f** was obtained in 46% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 8.46 (m, 1H), 8.38 (m, 1H), 7.71 (d, J = 8.7 Hz, 2H), 6.66 (m, 1H), 7.25 (m, 1H), 6.51 (d, J = 8.7 Hz, 2H), 4.38 (m, 2H), 2.76 (t, J = 7.2 Hz, 2H), 2.00 (t, J = 7.2 Hz, 2H), 1.66-1.44 (m, 4H), 1.26 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$)
δ 24.55, 25.01, 28.52, 28.59, 32.48, 37.49, 44.33, 111.44, 123.78, 126.00, 130.47, 134.64, 135.49, 147.76, 147.90, 151.85, 171.07,199.83.

Example 86:

***N*-Hydroxy-7-[4-(1-(4-phenylpiperazinyl))benzoyl]heptanamide (138g)**

Step 1: Ethyl-7-[4-(1-(4-phenylpiperazinyl))benzoyl]heptanoate (**136g**)

[0323] Following the procedure described in Example **80**, step 1, but substituting 1-phenylpiperazine for aniline, the title compound **136g** was obtained in 32% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J = 9.0 Hz, 2H), 7.33-7.26 (m, 3H), 6.97 (m, 2H), 6.92 (d, J = 9.0 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.51 (m, 4H), 3.34 (m, 4H), 2.88 (t, J = 7.5 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 1.72 (m, 2H), 1.63 (m, 2H), 1.49 (s, 9H),1.38 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$ δ 14.23, 24.59, 24.82, 28.98,
29.07, 34.29,37.93, 47.48, 49.06, 60.15, 113.62, 116.31, 120.27, 127.68, 129.22, 130.10, 1 50.93, 153.89, 173.78, 198.78.

Step 2: 7-[4-(1-(4-phenylpiperazinyl))-benzoyl]heptanoic acid (**137g**)

[0324] Following the procedure described in Example 18, step 3, but substituting ester **136g** for ester **49a**, the title compound **137g** was obtained in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 9.0 Hz, 2H), 7.25-7.17 (m, 3H), 6.89-6.78 (m, 5H), 6.92 (d, J = 9.0 Hz, 2H), 3.41 (m, 4H), 3.24 (m, 4H), 2.89 (t, J = 7.5 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.73 (m, 2H), 1.65 (m, 2H), 1.28 (m, 4H), ^{13}C NMR (75 MHz, $CDCl_3$)
δ 24.52, 24.57, 28.88, 29.02, 33.84, 37.90, 47.46, 49.10, 113.64, 116.37, 120.34, 127.64, 129.23, 130.14, 150.91, 153.91, 179.02, 198.88.

Step 3: *N*-Hydroxy-7-[4-(1-(4-phenylpiperazinyl))benzoyl]heptanamide (**138g**)

[0325] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **137g** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **138g** was obtained in 38% yield. ^{1}H NMR (300MHz, 20% CD_3OD in $CDCl_3$): δ 7.79 (d, J = 8.7 Hz, 2H), 7.19 (m, 2H), 6.89-6.78 (m, 5H), 3.41 (m, 4H), 3.24

(m, 4H), 2.78 (t, J = 7.5 Hz, 2H), 2.00 (t, J = 7.5 Hz, 2H), 1.66-1.46 (m, 4H),1.26 (m, 4H), ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$)
δ 24.40, 25.03, 28.61 (2), 32.48, 37.65, 47.06, 48.96, 113.35, 116.24, 120.22, 126.89, 128.9 8, 130.06, 150.65, 153.89, 171.11, 199.86.

Example 87:

***N*-Hydroxy-7-[4-(1-piperidinyl)benzoyl]heptanamide (138h)**

Step 1: Ethyl-7-[4-(1-piperidinyl)benzoyl]heptanoate (**136h**)

[0326] Following the procedure described in Example **80**, step 1, but substituting 1-piperidine for aniline, the title compound **136h** was obtained in 40% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 4.07 (q, J = 7.2 Hz, 2H), 3.30 (m, 4H), 2.81 (t, J = 7.5 Hz, 2H), 2.24 (t, J = 7.5 Hz, 2H), 1.74-1.56 (m, 10H), 1.20 (m, 4H), 1.24 (t, J =7.2Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.23, 24.32, 24.28, 24.81, 25.32, 28.97, 29.07, 34.28, 37.79, 48.58, 60.11,113.26, 126.40,130.13,154.29,173.77,198.63..

Step 2: 7-[4-(1-piperidinyl)benzoyl]heptanoic acid (**137h**)

[0327] Following the procedure described in Example 18, step 3, but substituting ester **136h** for ester **49a**, the title compound **137h** was obtained in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0 Hz, 2H), 3.35 (m, 4H), 2.86 (t, J = 7.5 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.74-1.56 (m, 10H), 1.20 (m, 4H). ^{13}C NMR (75 MHz, CDCl3) δ 24.25,24.46,24.65,25.24,28.81,28.97,33.92, 37.71, 48.53, 113.24,126.25,130.17,154.27,179.53,198.87.

Step 3: *N*-Hydrgxy-7-[4-(1-piperidinyl)benzoyl]heptanamide (**138h**)

[0328] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **137h** for **37,** and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **138h** was obtained in 45% yield. ^{1}HNMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.71 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 3.23 (m, 4H), 2.74 (t, J = 7.2 Hz, 2H),1.98 (t, J = 6.6 Hz, 2H), 1.54 (m, 10H), 1.24 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in CDCl3) δ 24.00, 24.50 24.99(2), 28.49, 28.58, 32.43, 37.49, 48.23,112.96,125.55,130.11,154.25,171.15,199.72.

Example 88:

***N*-Hydroxy-7-[4-(*N*-morpholinyl)benzoyl]heptanamide (138i)**

Step 1: Ethyl-7-[4-(*N*-morpholinyl)benzoyl]heptanoate (**136i**)

[0329] Following the procedure described in Example 80, step 1, but substituting morpholine for aniline, the title compound **136i** was obtained in 43% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.87 (m, 4H), 3.30 (m, 4H), 288 (t, J = 7.5 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H),1.72 (m, 2H), 1.63 (m, 2H), 1.38 (m, 4H), 1.25 (t, J = 7.2Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$)
δ14.21,24.52,24.78,28.94,29.03, 34.25,37.90,47.53,60.12,113.29,127.90,130.01, 154.06, 173.74, 198.75.

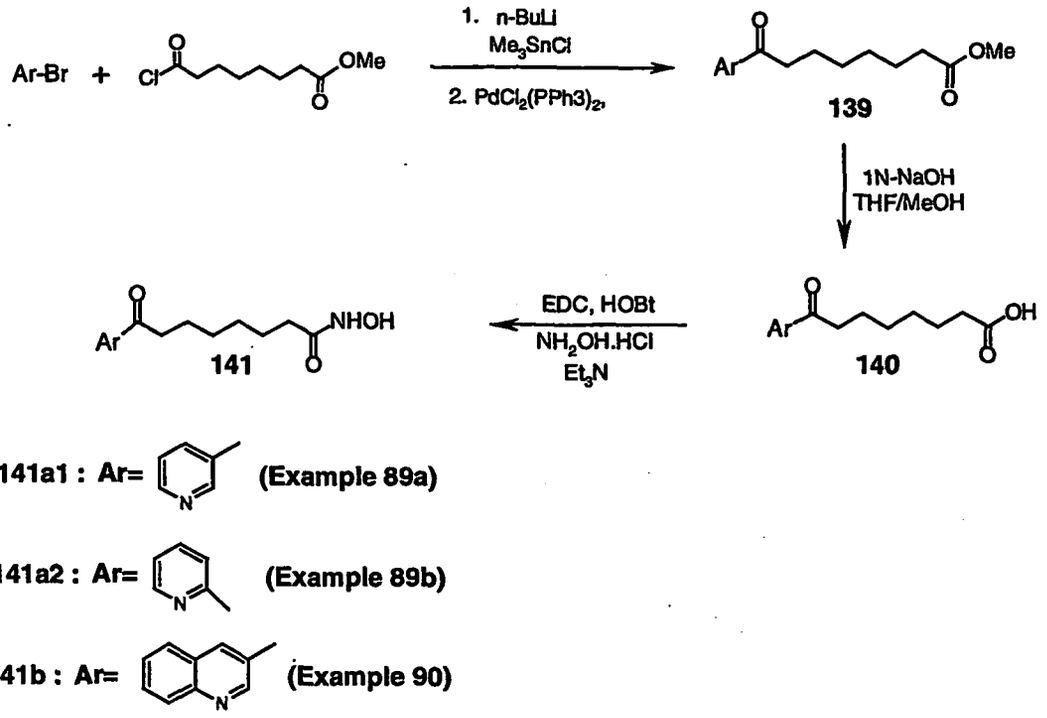
Step 2: 7-[4-(*N*-morpholinyl)benzoyl]heptanoic acid (**137i**)

[0330] Following the procedure described in Example 18, step 3, but substituting ester **136i** for ester **49a,** the title compound **137i** was obtained in 93%yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 3.85 (m, 4H), 3.29 (m, 4H), 2.87 (t, J = 7.5 Hz, 2H), 2.33 (t, J = 7.5 Hz, 2H), 1.76-1.58 (m, 4H), 1.38 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$)
δ 24.48, 24.51, 28.85, 28.98, 33.90, 37.88, 47.51, 66.51, 113.32, 127.86, 130.06, 154.09, 179.41, 198.92.

Step 3: *N*-Hydroxy-7-[4-(*N*-morpholinyl)benzoyl]heptanamide (**138i**)

[0331] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **137i** for **37,** and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **138i** was obtained in 34% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 7.89 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 3.87 (m, 4H), 3.33 (m, 4H), 2.90 (t, J = 7.2 Hz, 2H), 2.11 (t, J = 7.2 Hz, 2H), 1.76-1.58 (m, 4H), 1.37 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$)

δ 24.34, 25.00, 28.53, 28.58, 32.46, 37.64, 47.15, 66.28, 113.08, 127.20, 129.97, 154.07, 1 71.13, 199.87.



141a1 : Ar= **(Example 89a)**

141a2 : Ar= **(Example 89b)**

141b : Ar= **(Example 90)**

Example 89:

***N*-Hydroxy-7-[(3-pyridyl)carbonyl]heptanamide (141a1)**

Step 1: Methyl-7-[3-(pyridyl)carbonyl]heptanoate (**139a1**)

i) Preparation of tin compound

[0332] To a stirred solution of 3-bromopyridine (1.58 g,10 mmol) in anhydrous ethyl ether (100mL) at -78˚C was added n-butyl lithium (1.6M in hexane, 7.5 mL) via a syringe, and the resulting solution was stirred at -78˚C for 10 minutes. Trimethyltin chloride (2.39 g,12 mmol) was then added, and the mixture was stirred at -78˚C for 20 minutes, and then warmed to room temperature over 1 hour. The reaction mixture was diluted with hexanes (30mL) and washed with water. The organic phase was dried and concentrated to give the crude product which was purified by vacuum distillation (125 ˚C at 15-20 mmHg) to give 3-trimethylstannyl pyridine (1.93 g, 80% yield).

ii) Stille coupling

[0333] A mixture of 3-trimethylstannyl pyridine (from *i*) (1.89 g, 7.81 mmol) and methyl 8-chloro-8-oxooctanoate in benzene (20mL) was heated overnight at reflux in the presence of $PdCl_2(PPh_3)_2$ (274 mg, 0.39 mmol). After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and water. The combined organic layers were dried, and concentrated. Purification by flash chromatography (ethyl acetate / hexane =1/1) gave the desired product **139a1** (1.15 g, 59 % yield) as a light yellow solid. ^{1}H NMR (300 MHz, CD_3OD): δ 9.16 (d, J =1.8 Hz, 1H), 8.77 (dd, J = 4.8,1.8 Hz,1H), 8.23 (m,1H), 7.43 (dd, J = 7.8,4.8 Hz,1H), 3.67 (s, 3H), 2.99(t, J = 7.5 Hz, 2H), 2.32 (t, J = 7.5 Hz, 2H), 1.77 (m, 2H),1.65 (m, 2H), 1.41 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.66, 24.66, 28.78, 28.84, 33.89, 38.67, 51.41,123.58,132.11,135.27,149.54,153.31,174.06,198.96.

Step 2: 7-[3-(pyridyl)carbonyl]heptanoic acid (**140a1**)

[0334] Following the procedure described in Example 18, step 3, but substituting ester **139a1** for ester **49a**, the title compound **140a1** was obtained in 98% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in CD_3OD): δ 9.12 (d, J = 1.8 Hz,1H),

8.74 (dd, J = 4.8,1.8 Hz, 1H), 8.30 (m, 1H), 7.50 (dd, J = 7.8,4.8 Hz, 1H), 3.02 (t, J = 7.5 Hz, 2H), 2.32 (t, J = 7.5 Hz, 2H), 1.77 (m, 2H), 1.65 (m, 2H), 1.41 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in CD_3OD) δ 23.00, 24.01, 28.12, 28.18, 33.30, 38.09,123.42,131.81, 135.37,148.39,152.13,175.80,198.76.

Step 3: *N*-Hydroxy- 7-[3-(pyridyl)carbonyl]heptanamide (**141a1**)

[0335] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **140a1** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **141a1** was obtained in 26% yield. ^{1}H NMR (300MHz, 20% CD_3OD in CD_3OD): δ 9.12 (d, J = 1.5 Hz,1H), 8.74 (dd, J = 4.8,1.5 Hz,1H), 8.30 (m,1H), 7.50 (dd, J = 7.8, 4.8 Hz, 1H), 3.02 (t, J = 7.5 Hz, 2H), 2.12 (t, J = 7.5 Hz, 2H), 1.75 (m, 2H),1.65 (m, 2H), 1.40 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in CD_3OD) δ 23.39, 25.00, 28.44, 28.53, 32.48, 38.46,123.86,132.17,135.80, 148.83,152.61,171.06,199.31.

Example 89b:

***N*-Hydroxy-7-[(2-pyridyl)carbonyl]heptanamide (141a2)**

Step 3: *N*-Hydroxy-7-[2-(pyridyl)carbonyl]heptanamide (**141a2**)

[0336] Following the procedure described in Example 90, step 1, but substituting 2-bromopyridine for 3-bromopyridine and without addition of palladium (0) catalyst, followed by Example 18, step 3, but substituting ester **139a2** for ester **49a**, and then the resulting carboxylic acid was substituted for **37** in Example 14, step 3, using 1.1 equivalent of $NH_2OOH.HCl$ and triethylamine each, to afford the title compound **141a2** was obtained in 5% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 8.67 (m, 1H), 8.03 (dt, J = 7.8,1.2 Hz, 1H), 7.90 (m, 1H), 7.53 (m, 1H), 3.21 (t, J = 7.5 Hz, 2H), 2.10 (t, J = 7.2 Hz, 2H), 1.73 (m, 2H), 1.65 (m, 2H), 1.40 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$) δ 23.45, 25.07, 28.53, 28.58, 32.55, 37.40, 121.77, 127.12, 137.05, 148.65, 152.97,171.19, 202.24.

Example 90:

***N*-Hydroxy-7-[(3-quinolinyl)carbonyl]heptanamide (141b)**

Step 1: Methyl-7-[3-(quinnolinyl)carbonyl]heptanoate (**139b**)

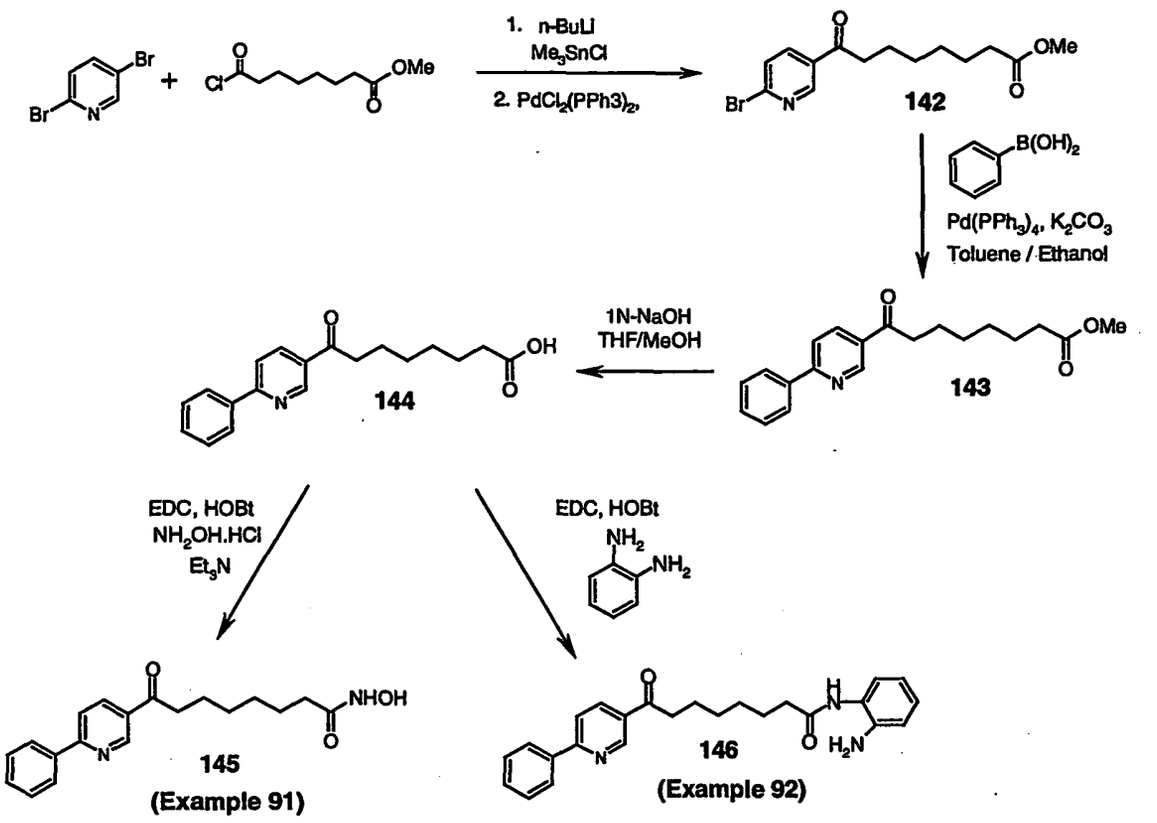
[0337] Following the procedure described in Example 90, step 1, but substituting 3-bromoquinoline for 3-bromopyridine, the title compound **140b** was obtained in 90% yield ^{1}H NMR (300MHz $CDCl_3$): δ 9.43 (d, J = 2.1 Hz, 1H), 8.71 (d, J = 2.1 Hz, 1H), 8.16 (m,1H), 7.97 (m, 1H), 8.84 (m, 1H), 7.63 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.10 (t, J =7.5 Hz, 2H), 2.31 (t, 7.5 Hz, 2H),1.81 (m, 2H), 1.66 (m, 2H), 1.43 (m, 4H), 1.25 (t, J =7.2 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 14.15, 23.77, 24.66, 28.82(2), 34.13, 38.68, 60.09, 126.78, 127.44, 129.03, 129.25, 131.82, 136.87, 148.97, 149.55, 173:59, 198.90.

Step 2: 7-[3-(quinolinyl)carbonyl]heptanoic acid (**140b**)

[0338] Following the procedure described in Example 18, step 3, but substituting ester **139b** for ester **49a**, the title compound **140b** was obtained in 93% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 9.25 (d, J = 2.1 Hz, 1H), 8.67 (d, J =1.8 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.89 (m, 1H), 7.76 (m, 1H), 7.56 (m, 1H), 3.01 (t, J = 7.5 Hz, 2H), 2.20 (t, J = 7.2 Hz, 2H), 1.70 (m, 2H), 1.54 (m, 2H), 1.33 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$) δ 23.60, 24.46, 28.62(2), 33.74, 38.55, 126.82, 127.65, 128.36, 128.99, 129.29, 132.19, 137.47, 148.58, 148.91,176.22, 199.23.

Step 3: *N*-Hydroxy-7-[3-(quinolinyl)carbonyl]heptanamide (**141b**)

[0339] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **140b** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **141b** was obtained in 43% yield.1H NMR (300 MHz, DMSO-d_6): δ 9.32 (d, J = 2.1Hz, 1H), 9.06 (d, J = 1.8 Hz, 1H), 8.20 (d, J = 7.2 Hz,1H), 8.09 (d, J = 8.7 Hz, 1H), 7.91 (m, 1H), 7.72 (m, 1H), 3.19 (t, J = 7.2 Hz, 2H), 1.95 (t, J = 7.5 Hz, 2H), 1.67 (m, 2H), 1.50 (m, 2H), 1.33 (m, 4H).



Example 91:

***N*-Hydroxy-7-[(5-(2-phenyl)pyrldyl)carbonyl]heptanamide (145)**

Step 1: Methyl-7-[(5-(2-bromo)pyridyl)carbonyl]heptanoate (**142**)

[0340] Following the procedure described in Example 89, step 1, but substituting 2,3-dibromopyridine for 3-bromopyridine, the title compound **142** was obtained in 39% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (d, J = 1.8 Hz, 1H), 8.77 (dd, J = 8.1, 2.4 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 3.63 (s, 3H), 2.91 (t, J = 7.5 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 1.71 (m, 2H), 1.60 (m, 4H), 1.35 (m, 4H).

Step 2: Methyl-7-[(5-(2-phenyl)pyridyl)carbonyl]heptanoate (**143**)

[0341] Following the procedure described in Example 67, step 1, but substituting respectively **142** for **49d** and phenyl boronic acid for 3-thiophene boronic acid, the title compound 143 was obtained in 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.23 (dd, J = 2.4, 0.9 Hz, 1H), 8.30 (dd, J = 8.7,2.4 Hz, 1H), 8.09-8.05 (m, 2H), 7.84 (dd, J = 8.7,0.9 Hz, 1H), 7.56-7.40 (m, 3H), 3.67 (s, 3H), 3.00 (t, J = 7.5 Hz, 2H), 2.32 (t, J = 7.5 Hz, 2H), 1.78 (m, 2H), 1.65 (m, 2H), 1.41 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$): δ 23.89, 24.73, 28.89, 28.93, 33.97, 38.74, 51.47, 120.24, 127.35, 128.93, 130.08, 130.45, 136.42,138.01,149.61,160.66,174.13,198.72

Step 3: 7-[(5-(2-Phenyl)pyridyl)carbonyl]heptanoic acid (**144**)

[0342] Following the procedure described in Example 18, step 3, but substituting ester **143** for ester **49a**, the title compound **144** was obtained in 90% yield. ^{1}H NMR (300MHz, 20% CD_3OD in $CDCl_3$): δ 9.08 (d, J = 1.8 Hz, 1H), 8.20 (dd, J = 8.7,1.8 Hz, 1H), 7.90 (m, 2H), 7.74(d, J = 8.7 Hz, 1H), 7.42-7.36 (m, 3H), 2.92 (t, J = 7.2 Hz, 2H), 2.17 (t, J = 7.5 Hz, 2H), 1.67 (m, 2H), 1.54 (m, 2H), 1.31 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$)
δ 23.66, 24.68, 28.65, 28.72, 34.31, 38.54, 120.54, 127.17, 128.73, 129.91, 130.31, 136.45, 137.79, 149.32, 160.82, 177.18, 199.18.

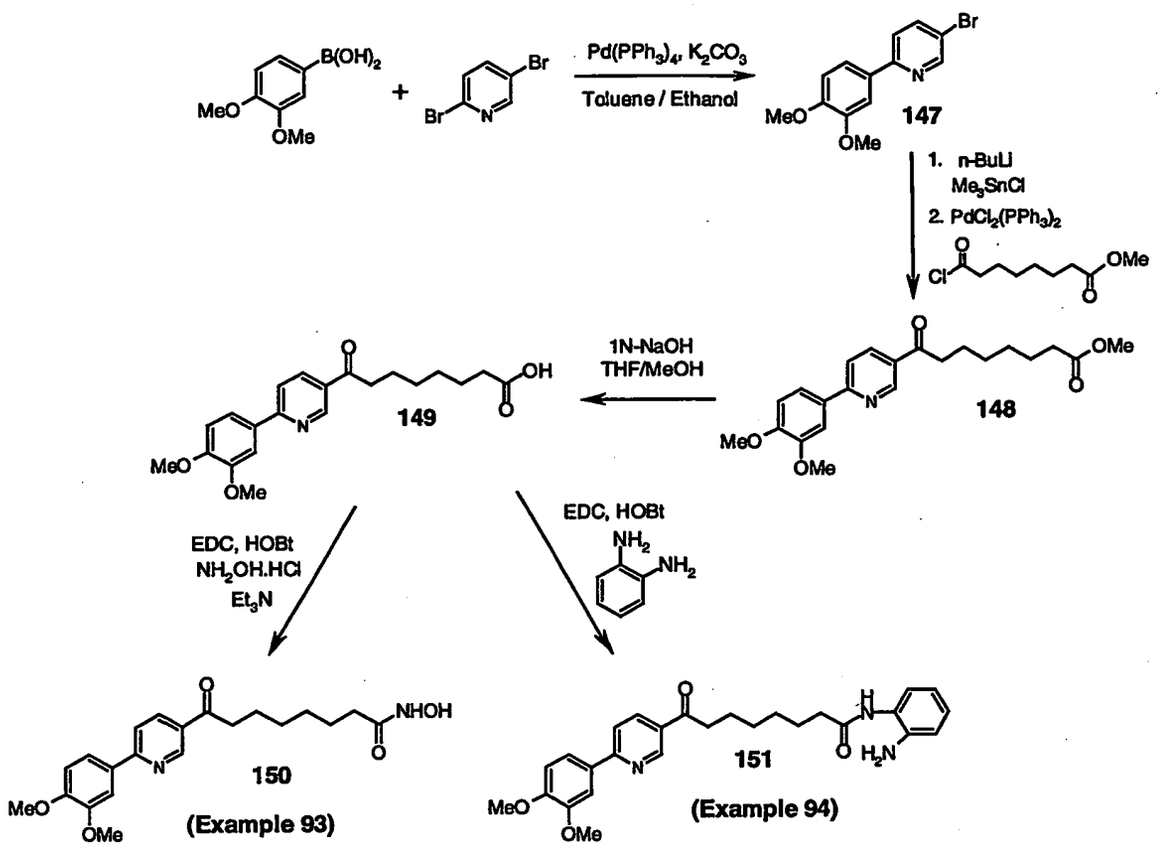
Step 4: *N*-Hydroxy-7-[(5-(2-phenyl)pyridyl)carbonyl]heptanamide (**145**)

[0343] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **144** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **145** was obtained in 33% yield. ^1H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 9.08 (d, J = 1.5 Hz, 1H), 8.20 (d, J = 8.4,1.5 Hz, 1H), 7.91-7.87 (m, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.46-7.35 (m, 3H), 2.91 (t, J = 7.5 Hz, 2H), 2.00 (br t, 2H), 1.66 (m, 2H), 1.54 (m, 2H), 1.30 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$: δ 23.60, 25.02, 28.50, 28.56,32.51, 38.47, 120.55, 127.16, 128.74, 129.93, 130.27, 136.45, 137.76, 149.31, 160.85, 171.05, 199.27.

Example 92:

***N*-(2-Aminophenyl)-7-[(5-(2-phenyl)pyridyl)carbonyl]heptanamide (146)**

[0344] Following the procedure described in Example 22, but substituting carboxylic acid **144** for **50g**, the title compound **146** was obtained in 42% yield. ^1H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 9.08 (dd, J = 2.1, 0.6 Hz, 1H), 8.21 (dd, J = 8.1, 2.1 Hz, 1H), 7.92-7.87 (m, 2H), 7.75 (dd, J = 8.1, 0.6 Hz, 1H), 7:46-7.35 (m, 3H), 7.03-6.91 (m, 2H), 6.72-6.64 (m, 2H), 2.94 (t, J = 7.5 Hz, 2H), 2.31 (t, J = 7.5 Hz, 2H), 1.74-1.58 (m, 4H), 1.36 (m, 4H). ^{13}C NMR (75 MHz, 20% CD_3OD in $CDCl_3$): δ 23.63, 25.40, 28.61, 28.74, 36.14, 38.51,117.84, 119.27, 120.55, 124.14, 125.35, 126.96, 127.18, 128.75, 129.93, 130.30, 136.46, 137.80, 140.58, 149.33, 160.87, 172.81, 199.30.



Example 93:

***N*-Hydroxy-7-[5-(2-(3,4-dimethoxyphenyl)pyridyl)carbonyl]heptanamide (150)**

Step 1: 2-(3 4-dimethoxyphenyl)-5-bromopyridine (**147**)

[0345] Following the procedure described in Example 67, step 1, but substituting respectively 2,5-dibromopyridine for **49d** and 3,4-dimethoxyphenyl boronic acid for 3-thiophene boronic acid, the title compound **147** was obtained in

78%Yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (dd, J = 2.4, 0.9 Hz, 1H), 7.77 (dd, J = 8.4,5.4 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.53 (dd, J = 8.4,0.9 Hz, 1H), 7.73 (dd, J = 8.4, 2.1 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.92, 55.93, 109.64, 111.01, 118.46, 119.25, 120.92, 131.05, 139.09, 149.28, 150.21, 1 50.36, 155.40.

Step 2: Methyl-7-[5-(2-(3,4-dimethoxyphenyl)pyridyl)carbonyl]heptanoate (**148**)

[0346] Following the procedure described in Example 89, step 1, but substituting 2-(3,4-dimethoxyphenyl)-5-bromopyridine for 3-bromopyridine, the title compound **148** was obtained in 78 % yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.12 (δ, J = 2.1 Hz,, 1H), 8.17 (dd, J = 8.4, 2.1 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.54 (dd, J = 8.4, 1.8 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.61 (s, 3H), 2.93 (t, J = 7.2 Hz, 2H), 2.27 (t, J = 7.5 Hz, 2H), 1.71 (m, 2H), 1.60 (m, 2H), 1.35 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$):
δ 23.90, 24.68, 28.86, 28.88, 33.91, 38.61, 51.42, 55.92, 55.93, 110.03, 110.96, 119.30, 120.08, 129.78, 130.91, 136.08, 149.30, 149.61, 150 .83,160.16, 174.08, 198.70.

Step 3: 7-[5-(2-(3,4-dimethoxyphenyl)pyridyl)carbonyl]heptanoic acid (**149**)

[0347] Following the procedure described in Example 18, step 3, but substituting ester **148** for ester **49a**, the title compound **149** was obtained in 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.20 (d, J =1.8 Hz, 1H), 8.25 (dd, J = 8.1,1.8 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 1.8 Hz, 1H), 7.57 (dd, J = 8.1,1.8 Hz, 1H), 6.96 (d,J = 8.1 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 2.99 (t, J = 7.2 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 1.77 (m, 2H), 1.66 (m, 2H), 1.41 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$):
δ 23.84, 24.46, 28.80, 28.81,
33.89, 38.60, 55.95, 55.96, 110.19, 110.04, 119.65, 120.24, 129.91, 130.72, 136.33,149.34 , 149.47, 150.91, 160.19, 179.04, 198.64.

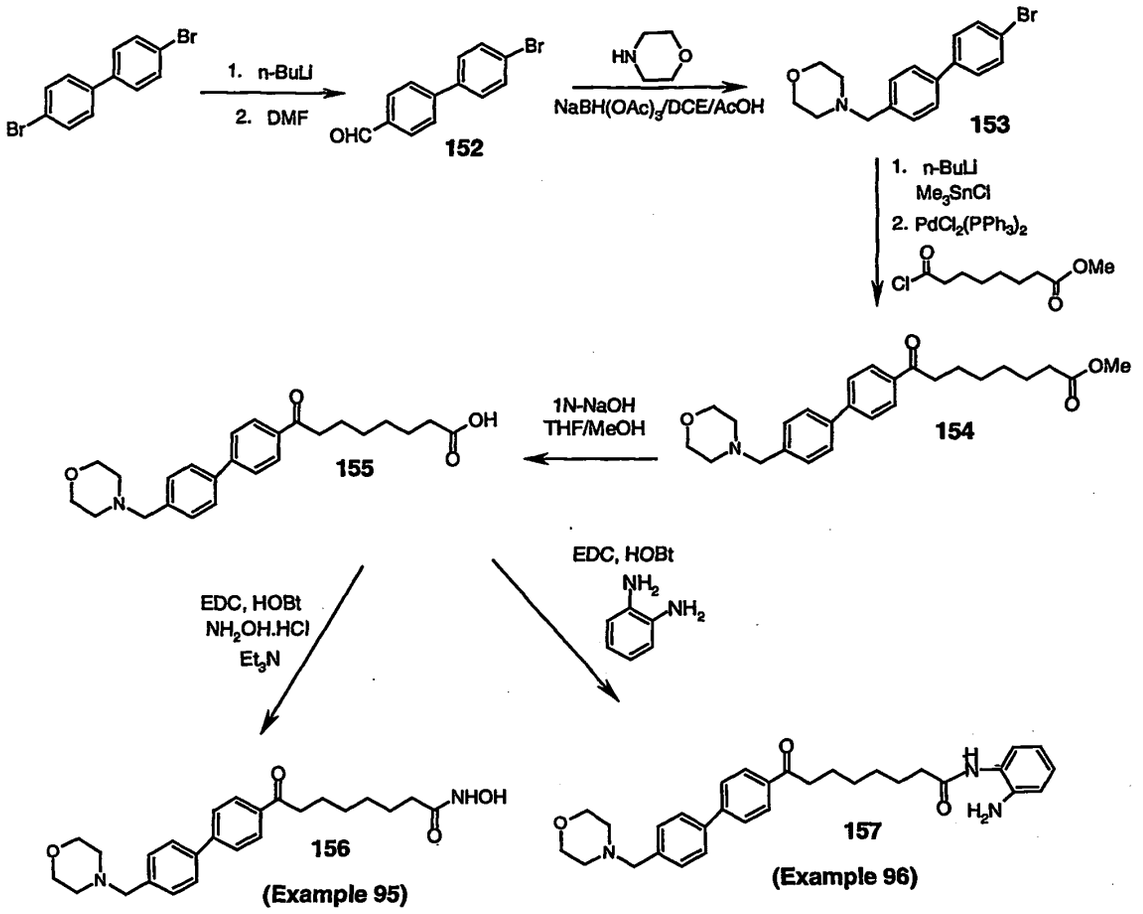
Step 4: *N*-Hydroxy-7-[5-(2-(3,4-dimethoxyphenyl)pyridyl)carbonyl]heptanamide (**150**)

[0348] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **149** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **150** was obtained in 32% yield. ^{1}H NMR (300 MHz, 20% CD_3OD in $CDCl_3$): δ 9.20 (br s, 1H), 8.25 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.63 (br s, 1H), 7.54 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 2.98 (t, J = 7.2 Hz, 2H), 2.06 (t, J = 7.2 Hz, 2H), 1.72 (m, 2H), 1.61 (m, 2H), 1.37 (m, 4H).

Example 94:

***N*-(2-Aminophenyl)-7-[5-(2-(3,4-dimethoxyphenyl)pyridyl)carbonyl]heptanamide (151)**

[0349] Following the procedure described in Example 22, but substituting carboxylic acid **149** for **50g**, the title compound **151** was obtained in 32%Yield. ^{1}H NMR (300MHz, $CDCl_3$): δ 9.18 (d, J =1.8 Hz, 1H), 8.23 (dd, J = 8.4, 2.1 Hz, 1H), 7.77 (d, J = 8.4,0.9 Hz, 1H), 7.73 (d, J = 2.1 Hz, 1H), 7.59 (dd, J = 8.4, 2.1 Hz, 1H), 7.35 (br s, 1H), 7.15 (m, 1H), 7.04 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H),6.78 (m, 2H), 4.00 (s, 3H), 3.95 (s, 3H), 2.99 (t, J = 7.2 Hz, 2H), 2.39 (t, J = 7.5 Hz, 2H), 1.72 (m, 4H), 1.44 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.71,25.38,28.69,28.81,36.39,38.42,55.78, 55.79, 109.94, 110.88,
117.68, 118.92, 119.16, 120.01, 124.08, 125.27, 126.83,129.58, 130.70, 135.96, 140.86, 149.13, 149.43, 150.69, 159.98, 171.95, 198.75.



Example 95:

***N*-Hydroxy-7-[4-(4-(*N*-methylmorpholinyl)phenyl)benzoyl]heptanamide (156)**

Step 1:4-(4-bromophenyl)benzaldehyde (**152**)

[0350] To a solution of 4',4-dibromobiphenyl (3.12 g,10 mmol) in dry THF (50 mL) at -78˚C was added dropwise a solution of n-BuLi (1.6M in hexane, 10 mmol). After addition, the mixture was stirred for 30 minutes at -78˚C. Anhydrous DMF (50 mL) was then added and the mixture was allowed to stir at room temperature for 2 hours. The solvent was removed under high vacuum and the residue was taken in water and extracted with dichloromethane (2 x 50 mL). The combined organic layer were dried ($MgSO_4$) and concentrated. Purification by flash chromatography (ethyl acetate/ hexane: 2/8) gave the title compound 152 55% yield. MS (ESI) = 261 (MH^+).

Step 2:(4-(*N*-methylmorpholinyl)phenyl)-4-bromophen (**153**),

[0351] To a solution of aldehyde **152** (2.6 g, 10 mmol) in 1,2-dichloroethane (20 mL), morpholine (0.737 g, 10.1 mmol) was added followed by sodium triacetoxyborohydride (2.2 g, 10.4 mmol) and then few drops of acetic acid. The mixture was stirred at room temperature for 4 hours and then quenched by addition of a saturated solution of sodium bicarbonate. The mixture was extracted with ethyl acetate, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (ethyl acetate/ hexane: 2/8) gave the title compound **153** (1.75 g, 55%yield). MS (ESI) = 333 (MH^+)

Step 3: Ethyl-7-[4-(4-(*N*-methylmorpholinyl)phenyl)benzoyl]heptanoate (**154**)

[0352] Following the procedure described in Example 89, step 1, but substituting **153** for 3-bromopyridine, the title compound **154** was obtained in 40 % yield.

MS (ESn - 424 (MH^+)

Step 4: 7-[4-(4-(*N*-methylmorpholinyl)phenyl)penzoyl]heptanoic acid (**155**)

[0353] Following the procedure described in Example 18, step 3, but substituting ester **154** for ester **49a**, the title compound **155** was obtained in 95% yield.
MS (ESI) = 410 (MH^+)

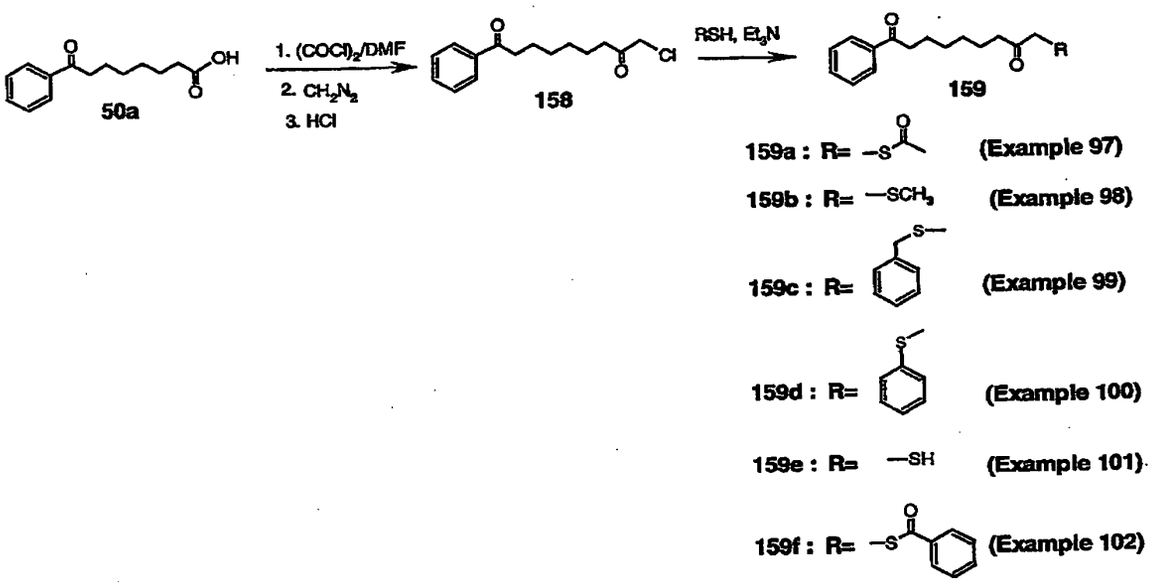
Step 5: *N*-Hydroxy-7-[4-(4-(*N*-methylmorpholinyl)phenyl)benzoyl]heptanamide (**156**)

[0354] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **155** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **156** was obtained in 20% yield. ^1H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.40-7.60 (m, 10H), 3.80 (m, 4H), 3.60 (s, 2H), 3.00 (m, 2H), 2.70 (m, 4H), 2.35 (m, 2H), 1.60 (m, 4H), 1.20 (m, 4H).

Example 96:

***N*-(2-Aminophenyl)-7-[4-(4-(*N*-methylmorpholinyl)phenyl)benzoyl]heptanamide (157)**

[0355] Following the procedure described in Example 22, but substituting carboxylic acid 155 for **50g**, the title compound **157** was obtained in 35 % yield. ^1H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.40-7.60 (m, 6H), 3.80 (m, 4H), 3.60 (s, 2H), 3.00 (m, 2H), 2.70 (m, 4H), 2.35 (m, 2H), 1.60 (m, 4H), 1.20 (m, 4H).



[0356] Example 101 is for illustration purpose only.

Example 97:

1-Acetylthio-2,9-dioxo-9-phenyl-nonane(159a)

Step 1: 1-chloxo-2 9-dioxo-9-phenyl-nonane (**158a**)

[0357] To a solution of the carboxylic acid **50a** (5 g, 0.02 mmol) in anhydrous dichloromethane (20 mL) under nitrogen was added dropwise, an excess of oxalyl chloride (5 mL, 0.06 mmol) neat followed by few drops of anhydrous DMF. The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was dried under high vacuum. The acid chloride was then taken in dry ether (20 mL) and to which was added a freshly prepared solution of diazomethane in ether. After addition the mixture was stirred at room temperature for four hours. The solvent was evaporated and the residue was treated with a solution of 4N HCl in dioxane (50 mL) at room temperature. After 4 hours

the dioxane was evaporated and the residue was taken in water and extracted with dichloromethane to give a residue which was chromatographed on silica gel to obtain the desired product **158a** (4 g, 75% yield). MS (ESI) = 267 (MH^+)

Step 2:1-Aceylthio-2,9-dioxo-9-phenyl-nonane (**159a**)

[0358] To a solution of the chloro ketone **158a** (300 mg, 1 mmol) in anhydrous dichloromethane (25 mL) was added at 0-5˚C a solution of the thiolacetic acid (92 mg, 1.2 mmol) in dichloromethane. The mixture was allowed to stir at room temperature for 18 hours. The mixture was then extracted from dichloromethane to give a residue, which was chromatographed on silica gel to obtain the desired product **159a** (103 mg, 50% yield). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.60-7.40 (m, 3H), 3.80 (s, 2H), 3.00 (m, 2H), 2.60 (m, 2H), 2.40 (s, 3H), 1.60 (m, 4H), 1.20 (m, 4H).

Example 98:

1-Methylthio-2,9-dioxo-9-phenyl-nonane (159b)

[0359] Following the procedure described in Example 97, step 1, 2, but substituting methanethiol for thiolacetic acid, the title compound **159b** was obtained in 60% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.40-7.60 (m, 3H), 3.20 (s, 2H), 3.00 (m, 2H), 2.60 (m, 2H), 2.10 (s, 3H), 1.60 (m, 4H), 1.20 (m, 4H).

Example 99:

1-Benzylthio-2,9-dioxo-9-phenyl-nonane (159c)

[0360] Following the procedure described in Example 97, step 1, 2, but substituting benzylthiol for thiolacetic acid, the title compound **159c** was obtained in 35% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.40-7.60 (m, 3H), 3.60 (s, 2H), 3.10 (s, 2H), 3.00 (m, 2H), 2.60 (m, 2H), 1.60 (m, 4H), 1.20 (m, 4H).

Example 100:

1-Phenylthio-2,9-dioxo-9-phenyl-nonane (159d)

[0361] Following the procedure described in Example 97, step 1, 2, but substituting phenylthiol for thiolacetic acid, the title compound **159d** was obtained in 50% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.20-7.60 (m, 8H), 3.60 (s, 2H), 3.00 (m, 2H), 2.60 (m, 2H), 1.60 (m, 4H), 1.20 (m, 4H).

Example 101:

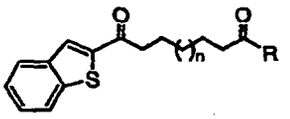
1-Mercapto-2,9-dioxo-9-phenyl-nonane (159e)

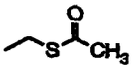
[0362] Following the procedure described in Example 97, step 1, 2, but substituting hydrogen sulfide for thiolacetic acid, the title compound **159e** was obtained in 30% yield.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.40-7.60 (m, 3H), 3.20 (d, J = 7.5 Hz, 2H), 3.00 (m, 2H), 2.60 (m, 2H), 1.80 (t, J = 7.5Hz), 1.60 (m, 4H), 1.20 (m, 4H).

Example 102:

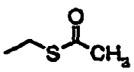
1-Benzoylthio-2,9-dioxo-9-phenyl-nonane (159f)

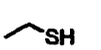
[0363] Following the procedure described in Example 97, step 1, 2, but substituting benzoylthiol for thiolacetic acid, the title compound **159f** was obtained in 52% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 4H), 7.60-7.40 (m, 6H), 4.00 (s, 2H), 3.00 (m, 2H), 2.60 (m, 2H), 1.60 (m, 4H), 1.20 (m, 4H).

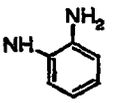


160 : n= 1, R=  (Example 103)

161 : n= 1, R=  (Example 104)

162 : n= 2, R=  (Example 105)

163 : n= 2, R=  (Example 106)

164 : n= 2, R=  (Example 107)

[0364] Examples 106 and 107 are for illustration purpose only.

Example 103:

1-Acetylthio-2,8-dioxo-8-(2-benzo[*b*]thiophene)-octane (160)

[0365] Following the procedure described in Example 18, step 1, 2, 3, but substituting respectively ethyl-6-iodohexanoate for ethyl-7-iodoheptanoate and 2-benzo[*b*]thiophene-carbonyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for 50a in Example 97, step 1, 2, to afford the title compound **160** obtained in 45%yield.^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.40-7.60 (m, 3H), 3.80 (s, 2H), 3.00 (m, 2H), 260 (m, 2H), 2.40 (s, 3H), 1.60 (m, 2H), 1.20 (m, 4H).

Example 104:

1-Mercapto-2,8-dioxo-8-(2-betizo[*b*]thiophene)-octane (161)

[0366] Following the procedure described in Example 18, step 1, 2, 3, but substituting respectively ethyl-6-iodohexanoate for ethyl-7-iodoheptanoate and 2-benzo[*b*]thiophene-carbonyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **50a** in Example 97, step 1, 2, and hydrogen sulfide for thiolacetic acid, to afford the title compound **161** obtained in 20%yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.40-7.60 (m, 3H), 3.20 (d, J = 7.5 Hz, 2H), 3.00 (m, 2H), 2.60 (m, 2H), 1.80 (t, J = 7.5 Hz, 1H), 1.60 (m, 2H), 1.20 (m, 4H).

Example 105:

2-Acetylthio-2,9-dioxo-9-(2-benzo[*b*]thiophene)-nonane (162)

[0367] Following the procedure described in Example 97, step 1, 2, but substituting carboxylic acid **50m** for **50a**, the title compound **162** was obtained in 50% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.60-7.40 (m, 3H), 3.80 (s, 2H), 3.00 (m, 2H), 260 (m, 2H), 2.40 (s, 3H), 1.60 (m, 4H), 120 (m, 4H).

Example 106:

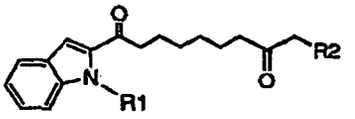
1-Mercapto-2,9-dioxo-9-(2-benzo[*b*]thiophene)-nonane (163)

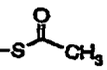
[0368] Following the procedure described in Example 97, step 1, 2, but substituting respectively carboxylic acid **50m** for **50a** and hydrogen sulfide for thiolacetic acid, the title compound **163** was obtained in 30% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.60-7.40 (m, 3H), 3.20 (d, J = 7.5 Hz, 2H), 3.00 (m, 2H), 2.60 (m, 2H), 1.80 (t, J = 7.5 Hz, 1H), 1.60 (m, 4H), 1.20 (m, 4H).

Example 107:

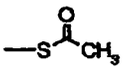
***N*-(2-Aminophenyl)-7-[(2-benzo[*b*]tbiophene)carbonyl]heptanamide (164)**

[0369] Following the procedure described in Example 22, but substituting carboxylic acid **50m** for carboxylic acid **50a**, the title compound **164** was obtained in 79% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00-7.60 (m, 6H), 7-7.20 (m, 3H), 2.80 (m, 2H), 2.00 (m, 2H), 1.60 (m, 4H), 1.20 (m, 4H).



165 : R1= CH_3, R2=  **(Example 108)**

166 : R1= CH_3, R2= —SH **(Example 109)**

167 : R1= H, R2=  **(Example 110)**

[0370] Example 109 is for illustration purpose only.

Example 108:

1-Acetylthio-2,9-dioxo-9-(2-(*N*-methyl)indolyl)-nonane (165)

[0371] Following the procedure described in Example 1, step 4, but substituting 1-methyl indole-2-carboxylic acid for **5**, followed by Example 18, step 2, 3, but substituting *N*-methyl indole-2-carbonyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **50a** in Example 97, step 1, 2, to afford the title compound **165** in 40% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 5H), 7.60-7.40 (m, 5H), 4.10 (s, 3H), 3.80 (s, 2H), 3.00 (m, 2H), 2.60 (m, 2H), 2.40 (s, 3H), 1.60 (m, 2H), 1.20 (m, 4H).

Example 109:

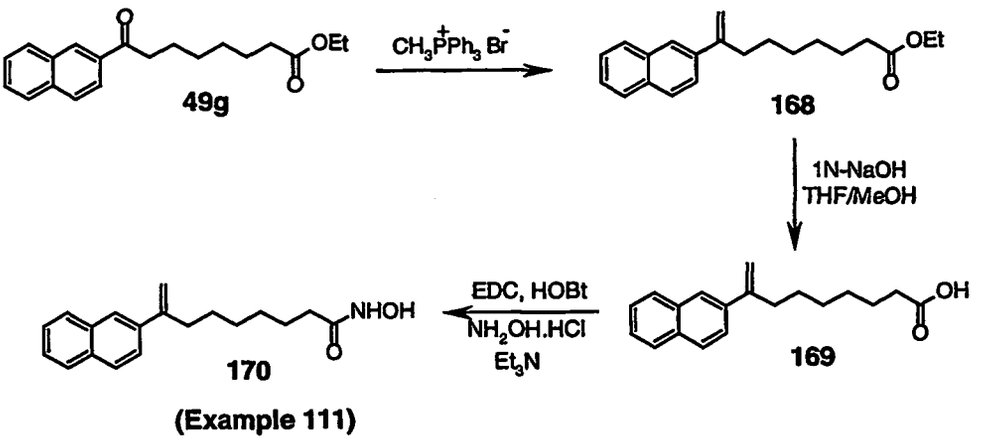
1-Mercapto-2,9-dioxo-9-(2-*N*-methylindolyl)-nonane (166)

[0372] Following the procedure described in Example 1, step 4, but substituting 1-methyl indole-2-carboxylic acid for **5**, followed by Example 18, step 2, 3, but substituting *N*-methyl indole-2-carbonyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **50a** in Example 97, step 1, 2, and hydrogen sulfide for thiolacetic acid, to afford the title compound **166** in 25% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.60-7.40 (m, 3H), 4.10(s, 3H), 3.20 (d, J = 7.5 Hz, 2H), 3.00 (m, 2H), 2.60 (m, 2H), 1.80 (t, J = 7.5 Hz, 1H), 1.60 (m, 4H),1.20 (m, 4H).

Example 110:

1-Acetylthio-2,9-dioxo-9-(2-indolyl)-nonane (167)

[0373] Following the procedure described in Example 1, step 4, but substituting indole-2-carboxylic acid for **5**, followed by Example 18, step 2, 3, but substituting indole-2-carbonyl chloride for benzoyl chloride, and then the resulting carboxylic acid was substituted for **50a** in Example 97, step 1, 2, to afford the title compound **167** in 60% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.40-7.60 (m, 3H), 3.80 (s, 2H), 3.00 (m, 2H), 2.60 (m, 2H), 2.40 (s, 3H), 1.60 (m, 2H), 1.20 (m, 4H).



(Example 111)

Example 111:

***N*-Hydroxy-8-(2-naphthyl)non-8-enamide (170)**

Step 1: Ethyl 8-(2-naphthy)non-8-enoate (**168**)

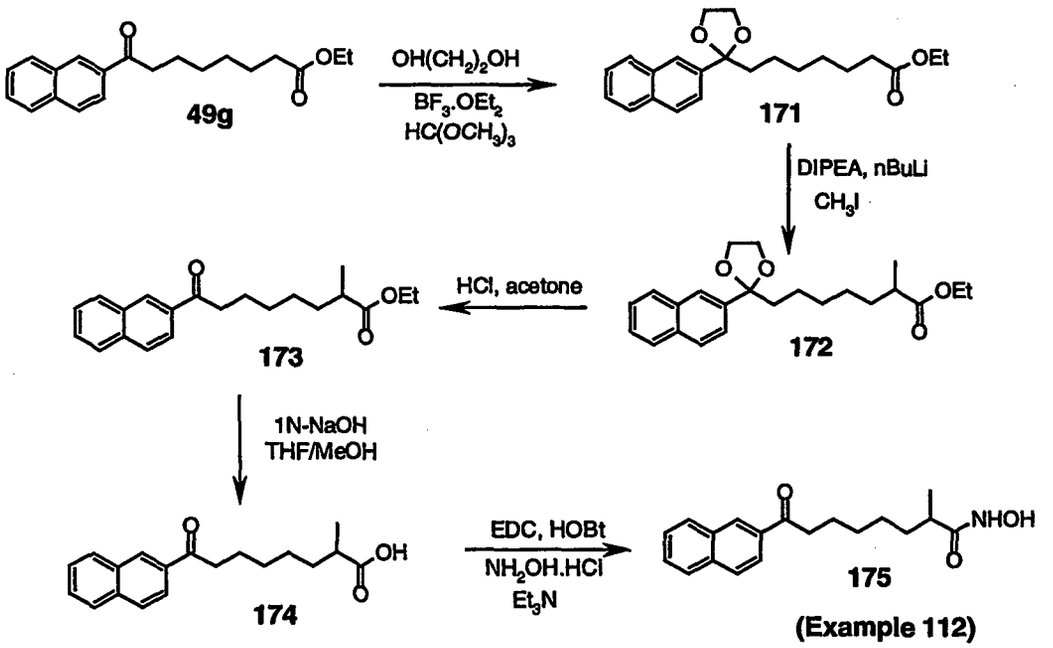
[0374] To a solution of methyltriphenylphosphonium bromide (469 mg,1.31 mmol) in THF (6 mL) pre-cooled to 0˚C under nitrogen atmosphere was added dropwise *n*-butyllithium (1.42M solution in hexanes, 905 μL, 1.28 mmol) and stirred over 20 minutes. To this a THF (4mL) solution of **49g** (82 mg, 0.262 mmol) was transferred *via cannula.* The yellow mixture was stirred over 30 minutes and quenched with a saturated aqueous solution of ammonium chloride, as the yellow color immediately disappeared. The solvent was removed by evaporation *in vacuo* and the aqueous residue was partitioned between water and ethyl acetate. The aqueous layer was then extracted with ethyl acetate and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by flash chromatography (5% to 8% diethyl ether in hexane) to afford the title compound **168** (43 mg) in 52% yield. ^1H NMR: ($CDCl_3$) δ: 7.85-7.78 (m, 4H), 7.58 (dd, J = 8.8,1.9 Hz, 1H), 7.48-7.44 (m, 2H), 5.42 (d, J = 1.1 Hz, 1H), 5.16 (d, J = 1.4 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.62 (t, J = 6.9 Hz, 2H), 2.28 (d, J = 7.4 Hz, 2H), 1.64-1.49 (m, 4H), 1.39-1.33 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H). MS (ESI) = 311 (MH^+).

Step 2 : 8-(2-Naphthyl)non-8-enoic acid (**169**)

[0375] Following a procedure analogous to that described in Example 18, step 3, but substituting ester **169** for ester **49a**, the title compound was obtained in 99%. ^1H NMR: ($CDCl_3$) δ: 7.83-7.77 (m, 4H), 7.57 (d, J = 8.8 Hz, 1H), 7.47-7.44 (m, 2H), 5.40 (s, 1H), 5.14 (s, 1H), 2.61 (t, J = 7.1 Hz, 2H), 2.33 (t, J = 7.4 Hz, 2H), 1.64-1.21 (m, 8H). MS (ESI) = 283 (MH^+).

Step 3: *N*-Hydroxy-8-(2-naphthyl)non-8-enamide (**170**)

[0376] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **169** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **170** was obtained in 33% yield. ^1H NMR: ($CDCl_3$) δ: 8.22 (br s, 1H), 7.80-7.77 (m, 4H), 7.56 (d, J = 8.5 Hz, 1H), 7.46-7.44 (m, 2H), 5.39 (s, 1H), 5.13 (s, 1H), 2.59 (t, J = 6.6 Hz, 2H), 2.05 (br s, 2H), 1.56-1.11 (m, 8H). HRMS: (calc.) 297.1729 (M+), (found) 297.1744.



Example 112:

***N*-Hydroxy-2-methyl-7-(2-naphthoyl)heptanamide (175)**

Step 1: Ethyl-8-(2-naphthyl)-8-[2-(1,3-dioxolyl)]octanoate (**171**)

[0377] To a solution of **49g** (4.52 g, 14.47 mmol) in dichloromethane (140 mL) was added ethylene glycol (8.07 mL, 144.7 mmol) followed by boron trifluoride etherate (3.67 mL, 28.94 mmol). The mixture was stirred for 1 hour at room temperature. Then trimethyl orthoformate (2.73 mL, 21.71 mmol) was added and the mixture was stirred overnight. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate and the layers were separated. The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by flash chromatography (15% to 20% ethyl acetate/hexane), to afford the title compound **171** in 44% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.91 (s, 1H), 7.87-7.81 (m, 3H), 7.54 (dd, J = 8.5,1.4 Hz, 1H), 7.49-7.46 (m, 2H), 4.12-4.03 (m, 4H), 3.82-3.78 (m, 2H), 2.23 (t, J = 7.4 Hz, 2H), 1.99-1.94 (m, 2H), 1.59-1.54 (m, 2H). MS (ESI) = 357(MH^+).

Step 2: Ethyl-2-methyl-8-(2-naphthyl)-8-[2-(1,3-dioxolyl)]octanoate (**172**)

[0378] To a solution of freshly distilled (over sodium hydride) diisopropylamine (550 μL, 3.93 mmol) in THF (40 mL) pre-cooled to 0˚C under nitrogen atmosphere was added dropwise *n*-butyllithium (1.2M solution in hexanes, 3.12 mL, 3.65 mmol). The mixture was stirred at 0˚C for 20 minutes and cooled down to -78˚C. Then a pre-cooled (-78˚C) solution of **171** (1.0 g, 2.81 mmol) in THF (15 mL) was transferred *via cannula.* The mixture was stirred for 1 hour at -78˚C. Then a pre-cooled (-78˚C) solution of iodomethane (349 μL, 5.61 mmol) in THF (15 mL) was transferred *via cannula.* The resulting mixture was stirred at -78˚C for 30 minutes, quenched with a saturated aqueous solution of ammonium chloride, and then warmed to room temperature. Water was added and the mixture was stirred for 4 hours, after which the THF layer had turned yellow. The mixture was concentrated *in vacuo* and the aqueous residue was partitioned between diethyl ether and water. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by flash chromatography (10% ethyl acetate in hexane) to afford the title compound **172** (950 mg) in 91% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.91 (s, 1H), 7.87-7.81 (m, 3H), 7.54 (dd, J = 8.8,1.9 Hz, 1H), 7.51-7.45 (m, 2H), 4.12-4.03 (m, 4H), 3.86-3.78 (m, 2H), 2.35 (sext, J = 7.1 Hz, 1H), 1.99-1.94 (m, 2H), 1.60-1.54 (m, 2H), 1.35-1.19 (m, 9H), 1.09 (d, J = 6.9 Hz, 3H). MS (ESI) = 371 (MH^+).

Step 3 : Ethyl-2-methyl-7-(2-naphthoyl)heptanoate (**173**)

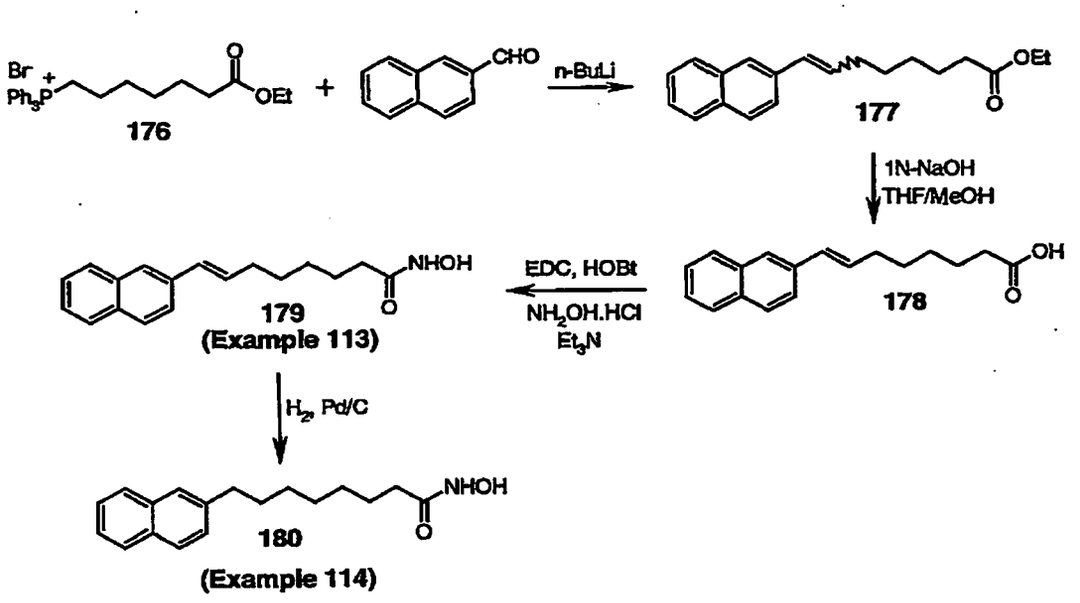
[0379] To a solution of **172** (950 mg, 2.56 mmol) in acetone (75 mL) was added an aqueous 1*N* solution of hydrochloric acid (15 mL) until a precipitate persisted, and then more acetone was added until a solution is obtained. The mixture was stirred at room temperature for 1 hour and then at 50°C for 1 hour. The mixture was concentrated *in vacuo* to a 10 mL volume. The white precipitate formed was filtered, rinsed with water to give **173**. ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 8.47 (s, 1H), 8.04-7.96 (m, 2H), 7.91-7.86 (m, 2H), 5.57 (quint d, J=7.7,1.9 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.09 (t, J = 7.4 Hz, 2H), 2.46-2.39 (m, 1H), 1.82-1.51 (m, 4H), 245-234 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H). MS (ESI) = 327 (MH^+).

Step 4: 2-Methyl-7-(2-naphthoyl)heptanoic acid (**174**)

[0380] Following a procedure analogous to that described in Example 18, step 3, but substituting ester **173** for ester **49a**, the title compound **174** was obtained in 73%. ^{1}H NMR (300MHz, $CDCl_3$) δ: 8.47 (s, 1H), 8.03 (dd, J = 8.5, 1.6 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.57 (quint d, J = 7.7,1.9 Hz, 2H), 3.10 (t, J = 7.1 Hz, 2H), 2.52-2.46 (m, 1H), 1.83-1.72 (m, 4H), 1.52-1.42 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H). MS (ESI) = 299 (MH^+).

Step 5 : *N*-Hydroxy-2-methyl-7-(2-naphthoyl)heptanamide (**175**)

[0381] Following a procedure analogous to that described in Example 14, step 3, but substituting carboxylic acid **174** for 37, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **175** was obtained in 65%. ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 8.47 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.91-7.86 (m, 2H), 7.63-7.55 (m, 2H), 3.18-3.02 (m, 2H), 2.31-2.17 (m, 1H), 1.73-1.694 (m, 2H), 1.50-1.28 (m, 4H), 1.11-1.07 (m, 3H). HRMS: (calc.) 313.1678, (found) 313.1685.



[0382] Examples 113 and 114 are for illustration purpose only.

Example 113:

(*E*)-*N*-Hydroxy-8-(2-naphthyl)-7-octenamide (179)

Step 1: (Carbethoxyhexyl)triphenylphosphonium bromide (**176**)

[0383] To a solution of ethyl 7-bromoheptanoate (10.0 g, 42.17 mmol) in toluene (280 mL) was added solid triphenylphosphine (11.06 g, 42.17 mmol). The solution was refluxed over 24 hours under nitrogen atmosphere and then cooled to room temperature. The supernatant was transferred into a different flask and an excess of triphenylphosphine (5.53

g, 21.09 mmol) was added. The solution was refluxed over 3 days and cooled to room temperature without stirring to favor sedimentation. The supernatant again removed by decantation and the resulting colorless oil was dried over high vacuum affording the title compound **176** (18.24 g) in 87% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.96-7.62 (m, 9H), 7.37-7.08 (m, 6H), 4.11-4.00 (m, 2H), 3.86-3.70 (m, 2H), 2.37-2.32 (m, 4H), 2.28-219 (m, 2H), 1.72-1.46 (m, 6H), 1.31-1.25 (m, 2H), 1.22-1.15 (m, 3H). MS (ESI) = 419 (Phosphonium Ion).

Step 2: (E/2)-Ethyl 8-(2-naphthyl)-7-octenoate (**177**)

[0384] To a suspension of phosphonium salt **176** (18.14 g, 36.32 mmol) in THF (300 mL) pre-cooled to 0˚C was added dropwise *n*-butyllithium (1.13M solution in hexanes, 35.4 mL, 39.95 mmol). The resulting light yellow solution was stirred at 0˚C over 30 minutes and a solution of a 2-naphthaldehyde (5.67 g, 36.32 mmol) in THF (60 mL) was transferred dropwise *via cannula.* The mixture was stirred overnight, allowing to warm to room temperature. The reaction was quenched with a saturated aqueous solution of ammonium chloride. Most of the THF was removed by evaporation *in vacuo* and the aqueous residue was partitioned between diethyl ether and water. The aqueous layer was extracted with diethyl ether and the combined organic layers were successively washed with water, brine, dried over magnesium sulfate and concentrated. The crude residue was purified by flash chromatography (6% to 8% ethyl acetate in hexane) affording the title compound **177** in 34% yield as a mixture of *E* and *Z* isomers. ^{1}H NMR: ($CDCl_3$) δ: 7.83-7.75 (m, 3H), 7.71 (s, 0.5H), 7.67 (s, 0.5H), 7.57 (dd, J = 8.5,1.9 Hz, 0.5H), 7.49-7.38 (m, 2.5H), 6.57 (d, J = 11.5 Hz, 0.5H), 6.54 (d, J =15.9 Hz, 0.5H), 6.34 (dt, J =15.7, 7.1 Hz, 0.5H), 5.73 (dt, J =11.8, 7.1 Hz, 0.5H), 4.17-4.10 (m, 2H), 2.42 (qd), J = 7.4,1.9 Hz, 1H), 2.34-2.24 (m, 3H), 1.73-1.31 (m, 6H), 1.28-1.22 (m, 3H). MS (ESI) = 297 (MH^+).

Step 3: (E)-8-(2-Naphthyl)-7-octenoic acid (178)

[0385] Following a procedure analogous to that described in Example 18, step 3, but substituting ester **177** for ester **49a**, the title compound **178** was obtained in 60%. ^{1}H NMR: ($CDCl_3$) δ: 7.79-7.75 (m, 3H), 7.67 (s, 1H), 7.57 (dd, J = 8.5,1.7 Hz, 1H), 7.47-7.38 (m, 2H), 6.54 (d, J =15.7 Hz, 1H), 6.34 (dt, J = 9.0,6.6 Hz, 1H), 2.38 (t, J = 7.4 Hz, 2H), 2.28 (q, J = 6.6 Hz, 1H), 1.74-1.64 (m, 2H), 1.57-1.40 (m, 4H). MS (ESI) = 269 (MH^+).

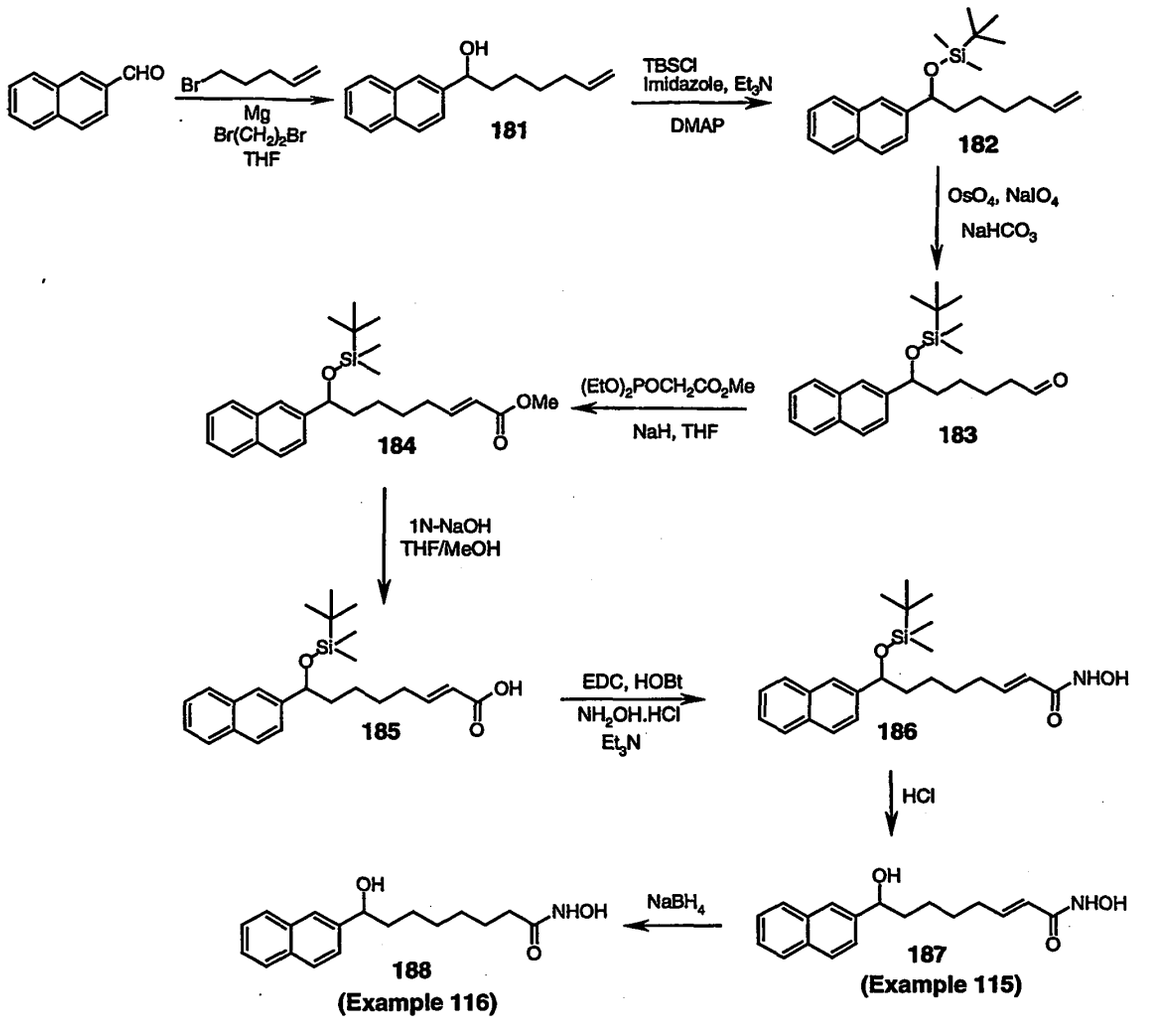
Step 4: (E)-*N*-Hydroxy-8-(2-naphthyl)-7-octenamide (**179**)

[0386] Following a procedure analogous to that described in Example 14, step 3, but substituting carboxylic acid **178** for 37, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **179** was obtained in 37% yield. ^{1}H NMR: (CD_3OD) δ: 7.79-7.74 (m, 3H), 7.67 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.45-7.36 (m, 2H), 6.56 (d, J =15.7 Hz, 1H), 6.38 (dt, J = 15.7,6.9 Hz, 1H), 2.28 (q, J = 6.3 Hz, 2H), 2.11 (t, J = 7.4 Hz, 2H), 1.72-1.62 (m, 2H), 1.58-1.50 (m, 2H), 1.46-1.40 (m, 2H). HRMS (calc.): 283.1572, (found): 283.1567.

Example 114:

***N*-Hydroxy-8-(2-naphthyl)octanamide (180)**

[0387] To a solution of compound **179** (30 mg, 0.106 mmol) in methanol (2 mL) was added a catalytic amount of 10% palladium on charcoal. The mixture was degassed and applied under hydrogen atmosphere and stirred for 15 minutes. Hydrogen was evacuated by vacuum and the mixture was filtered through Celite and rinsed with methanol. The filtrate was concentrated *in vacuo,* affording the title compound **180** (29.1 mg) in 97% yield. ^{1}H NMR: (300 MHz, CD_3OD) δ: 7.80-7.74 (m, 3H), 7.60 (s, 1H), 7.44-7.37 (m, 2H), 7.33 (dd, J = 8.2,1.6 Hz, 1H), 2.77 (t, J = 7.4 Hz, 2H), 2.07 (t, J = 7.1 Hz, 2H), 1.71-1.64 (m, 2H), 1.62-1.57 (m, 2H), 1.37-1.28 (m, 6H). HRMS (calc.): 285.1729, (found): 285.1727.



Example 115:

***N*-Hydroxy-8-hydroxy-8-(2-naphthyl)-2-octenamide (187)**

Step 1: 1-(2-Naphthyl)-6-heptenol (**181**)

[0388] A flame-dried round-bottomed flask was charged with magnesium turnings (1.23 g, 50.75 mmol) and stirred under vacuum for 15 minutes and then applied under nitrogen atmosphere. THF (70 mL) was added followed by 1,2-dibromoethane (381 mg, 2.03 mmol), and the mixture was brought to the boiling point for 1 minute, then and cooled down to room temperature. A solution of 6-bromohexene (8.28 g, 50.75 mmol) in THF (30 mL) was transferred *via cannula* to the magnesium flask and the mixture was refluxed overnight and cooled to -78˚C. A solution of 2-naphthaldehyde (6.10 g, 39.04 mmol) in THF (30 mL) was transferred *via cannula* to the Grignard reagent and the mixture was slowly warmed to 0˚C over 3 hours and kept at that temperature for 2 hours. The reaction was quenched with a saturated aqueous ammonium chloride solution and THF was evaporated *in vacuo.* The aqueous residue was poured into a separating funnel containing water and the compound was extracted with diethyl ether (2 x 100 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography (10% to 15% ethyl acetate in hexane), affording the title compound **181** in 89% yield (8.33g). ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.85-7.78 (m, 4H), 7.51-7.44 (m, 3H), 5.85-5.72 (m, 1H), 5.02-4.91 (m, 2H), 4.87-4.82 (m, 2H), 2.08-2.01 (m, 2H), 1.94-1.80 (m, 2H), 1.53-1.23 (m, 4H). MS (ESI) = 223 (MH^+-H_2O).

Step 2: O-(t-Butyldimethylsilyl)-1-(2-naphthyl)-6-heptenol (**182**)

[0389] To a solution of alcohol **181** (1.0g, 4.16 mmol) in dichloromethane (40mL) at room temperature under nitrogen atmosphere were successively added solid *t*-butyldimethylsilyl chloride (815 mg, 5.41 mmol), imidazole (340 mg, 4.99 mmol), and a catalytic amount of 2,6-dimethylaminopyridine. The mixture was stirred over 1 hour and triethylamine (696 μL, 4.99 mmol) was added. The mixture was stirred for 2 days. The reaction was quenched with water and the layers separated. The aqueous layer was extracted with dichloromethane and the combined organic layers were washed successively with a 1N HCl (2 x 10 mL), a saturated solution of sodium bicarbonate and brine, dried ($MgSO_4$) and concentrated *in vacuo.* The crude residue was purified by flash chromatography using hexane as the eluent, and affording the title compound **182** in 84% yield (1.24 g). ^1H NMR: (300 MHz, $CDCl_3$) δ: 7.83-7.79 (m, 3H), 7.70 (s, 1H), 7.47-7.40 (m, 3H), 5.78 (ddt, J =17.0,10.4, 6.6 Hz, 1H), 5.85-5.71 (m, 2H), 4.79 (dd, J= 6.9,4.9 Hz, 1H), 2.04-1.98 (m, 2H), 1.80-1.54 (m, 2H), 0.90 (s, 9H), 0.04 (s, 3H), -0.14 (s, 3H). MS (ESI) = 223 (MH^+-TBSO).

Step 3: 6-t-Butyldimethylsilyloxy-6-(2-naphthyl)hexanal (**183**)

[0390] To a solution of alkene **182** (1.05 g, 3.23 mmol) in *t*-butyl alcohol (50mL) were successively added water (10 mL), solid sodium bicarbonate (2.71 g, 32.3 mmol), sodium periodate (4.15 g, 19.38 mmol), and osmium tetroxide (8 mg, 0.032 mmol). The mixture turned light brown and a precipitate formed in large amount, making magnetic stirring impossible so the mixture was shaken by hand every 10 minutes for 3.5 hours and the brownish color almost disappeared. The reaction was quenched with a 10% aqueous solution of sodium thiosulfate. After 30 minutes, the white precipitate was filtered off and rinsed with diethyl ether. The filtrate was concentrated in *vacuo.* The residue was partitioned between diethyl ether and water. The aqueous layer was extracted (2 x 50 mL) with diethyl ether. The combined organic layers were washed successively with a 10% aqueous solution of sodium thiosulfate, water and brine, dried ($MgSO_4$), and concentrated *in vacuo,* yielding the title compound **183** as a crude oil in 91% yield (1.05 g). ^1H NMR: (300 MHz, $CDCl_3$) δ: 9.73 (t, J = 1.9 Hz, 1H), 7.83-7.78 (m, 3H), 7.69 (s, 1H), 7.49-7.43 (m, 3H), 4.80 (t, J = 6.9 Hz, 1H), 2.39 (td, J = 7.1, 1.6 Hz, 2H), 1.81-1.55 (m, 4H), 1.43-1.25 (m, 2H) 0.90 (s, 9H), 0.04 (s, 3H), -0.15 (s, 3H). MS (ESI) 225 (M+1-TBSO).

Step 4: methyl 8-t-butyldimethylsilyloxy-8-(2-naphthyl)-2-octenoate (**184**)

[0391] To a suspension of sodium hydride (60% in mineral oil, 177 mg, 4.42 mmol) in THF (25 mL) at room temperature under nitrogen atmosphere was added dropwise neat methyl diethylphosphonoacetate (811 μL, 4.42 mmol). The resulting solution was stirred for 10 minutes while cooling down to 0˚C. A solution of crude aldehyde **183** (1.05 g, 2.94 mmol) in THF (10 mL) was transferred *via cannula.* The resulting solution was stirred for 15 minutes at 0˚C and quenched with a saturated aqueous solution of ammonium chloride. The THF was evaporated *in vacuo* and the aqueous residue was partitioned between diethyl ether and water. The aqueous layer was extracted with diethyl ether and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* The crude residue was purified by flash chromatography

[0392] (5% ethyl acetate/hexane), affording the title compound **184** in 63% yield (1.30 g). ^1H NMR: (300 MHz, $CDCl_3$) δ: 7.83-7.78 (m, 3H), 7.69 (s, 1H), 7.49-7.41 (m, 3H), 6.94 (dt, J = 15.4, 7.1 Hz, 1H), 5.79 (dt, J = 15.7, 1.1 Hz, 1H), 4.79 (dd, J = 7.1,5.2 Hz, 1H), 3.71 (s, 3H), 2.16 (q, J = 7.4 Hz, 2H), 1.81-1.62 (m, 2H), 1.48-1.26 (m, 4H), 0.90 (s, 9H), 0.04 (s, 3H), -0.15 (s, 3H). MS (ESI) = 413 (MH^+).

Step 5: 8-t-Butyldimethylsilyloxy-8-(2-naphthyl)-2-octenoic acid (**185**)

[0393] Following a procedure analogous to that described in Example 18, step 3, but substituting ester **184** for ester **49a**, the title compound **185** was obtained in 100%. ^1H NMR: ($CDCl_3$) δ: 7.83-7.78 (m, 3H), 7.72 (s, 1H), 7.48-7.40 (m, 3H), 6.74 (dt, J =15.4, 7.1 Hz, 1H), 5.78 (d, J = 15.4 Hz, 1H), 4.88-4.84 (m, 1H), 2.17-2.11 (m, 2H), 1.82-1.69 (m, 2H), 1.471.28 (m, 4H), 0.89 (s, 9H), 0.06 (s, 3H), -0.16 (s, 3H). MS (ESI) = 421 (M^++Na).

Step 6: *N*-Hydroxy-8-t-butyldimethylsilyloxy-8-(2-naphthyl)-2-octenamide (**186**)

[0394] Following a procedure analogous to that described in Example 14, step 3, but substituting carboxylic acid **185** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **186** was obtained in 44% yield. ^1H NMR: (CD_3OD) δ: 7.83-7.72 (m, 4H), 7.48-7.40 (m, 3H), 6.77 (dt, J = 15.1, 7.1 Hz, 1H), 5.75 (d, J = 15.4 Hz, 1H), 4.91-4.79 (m, 1H), 2.18-2.14 (m, 2H), 1.79-1.68 (m, 2H), 1.48-1.39 (m, 2H), 1.28-1.21 (m, 2H), 0.89 (s, 9H), 0.06 (s, 3H), -0.16 (s, 3H). MS (ESI) = 436 (M^++Na).

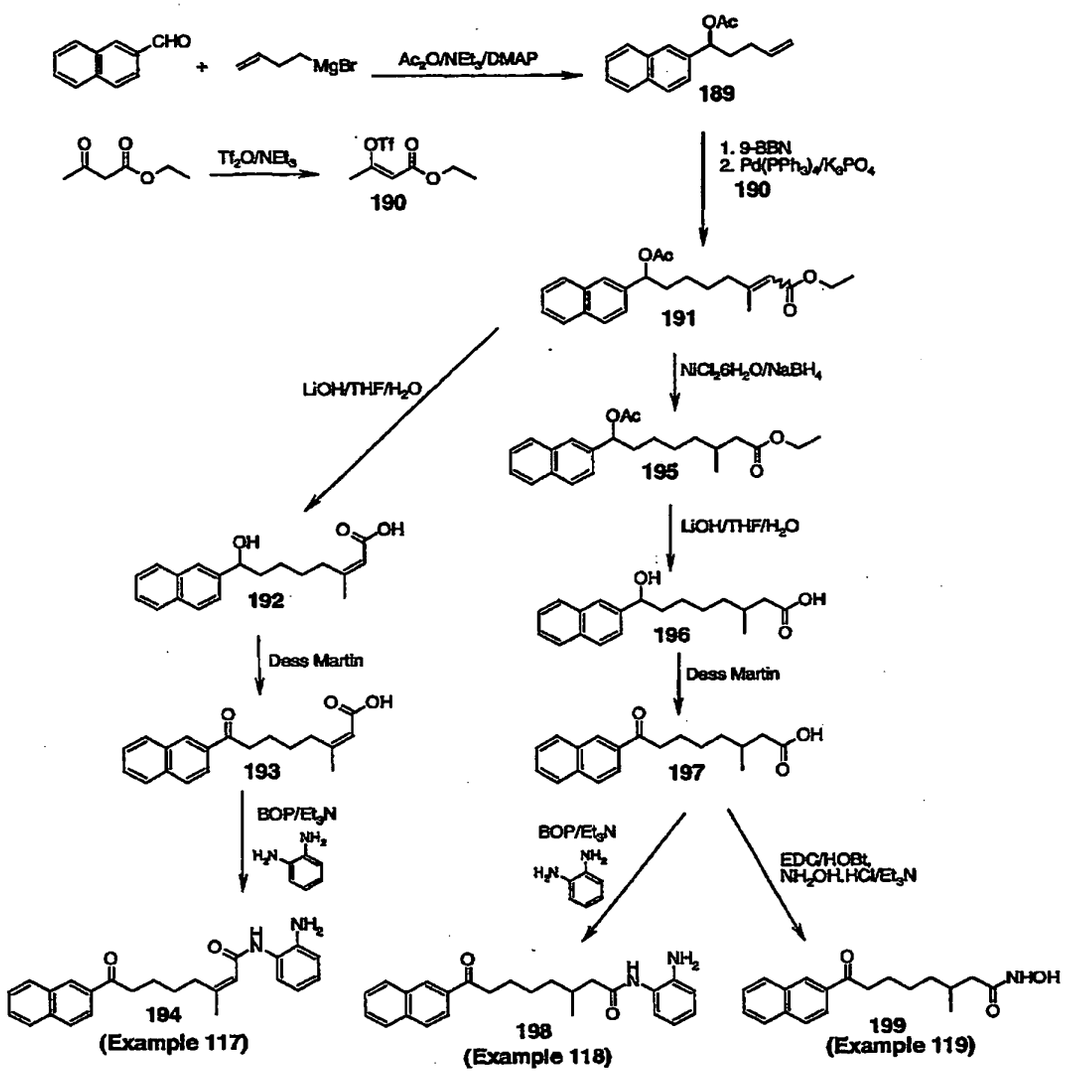
Step 7: *N*-Hydroxy-8-hydroxy-8-(2-naphthyl)-2-octenamide (**187**)

[0395] To a solution of the silyl ether **186** (300 mg, 0.725 mmol) in THF (3mL) at room temperature was added 1N aqueous solution of hydrochloric acid (3mL). The mixture was stirred for 3 hours at 30˚C and then added a large volume of ethyl acetate and water. The water layer was washed with ethyl acetate and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* The crude residue was purified by flash chromatography (75% to 100% ethyl acetate/hexane) affording unsatisfactory purity. So the compound was purified again using 8% methanol in dichloromethane affording the title compound **187** in 33% yield (77 mg). ^{1}H NMR: (300 MHz, CD_3OD) δ: 7.87-7.71 (m, 4H), 7.52-7.40 (m, 3H), 6.77 (dt, J =15.1, 6.9 Hz, 1H), 5.75 (d, J =15.1 Hz, 1H), 4.76 (t, J = 6.9 Hz, 1H), 2.17-2.10 (m, 2H), 1.84-1.77 (m, 2H), 1.49-1.27 (m, 4H) 1.88-1.75 (m, 4H). MS (ESI) = 282 (M^+-OH), 322 (M^++Na).

Example 116:

***N*-Hydroxy-8-hydroxy-8-(2-naphthyl)octanamide (188)**

[0396] To a solution of **187** (20 mg, 0.067 mmol) in methanol (670 μL) was added solid sodium borohydride (2.5 mg, 0.067 mmol). The mixture was stirred for 15 minutes and the solvent was evaporated *in vacuo.* The residue was partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash silica gel chromatography (6% methanol in dichloromethane) afforded the title compound **188** in 46% yield (9.1 mg). ^{1}H NMR: (300 MHz, CD_3OD) δ: 7.84-7.76 (m, 4H), 7.50-7.40 (m, 3H), 4.75 (t, J = 6.6 Hz, 1H), 2.05 (t, J = 7.4 Hz, 2H),1.86-1.76 (m, 2H), 1.62-1.55 (m, 2H), 1.43-1.23 (m, 6H). HRMS: (calc.) 283.1572 (M-H_2O), (found) 283.1581.



[0397] Example 117 is for illustration purpose only.

Example 117:

(*Z*)-*N*-(2-Aminophenyl)-3-methyl-7-(2-naphthoyl)-2-heptenamide (194)

Step 1-1-*O*-Acetyl-2-naphthyl-4-pentenol (**189**)

[0398] Following a procedure analogous to that described in Example 115, step 1, but substituting 4-bromobutene for 6-bromohexene, the resulting alcohol (2.16g, 10.16 mmol) was dissolved in dichloromethane (80 ml) and was added Et_3N (5.7 ml, 40.6 mmol), acetic anhydride (29 ml, 30.5 mmol) and DMAP (62 mg, 5%) at 0˚C. The solution was warmed up at room temperature and stirred for 5 hours. The resulting solution was washed with a saturated solution of $NaHCO_3$ (2 x 50 mL), brine and then dried over Na_2SO_4 and concentrated to give the product **189** (2.6g, 99%). ^{13}C NMR: (75 MHz, CDC13) δ: 21.2,29.6,35.2,75.5,115.2,124.2,125.7, 125.9,126.1,127.6,127.9,128.2,133.0,133.0,137.3,137.7,170.2 MS (ESI) = 277 (M^++Na).

Step 2: (*E*/*Z*)-Ethyl-3-trifluoromethanesulfonyloxy-2-butenoate (**190**)

[0399] To a solution of ethyl acetoacetate (545 μl, 5mmol) in dichloromethane at -78˚C was added Et_3N (2.1 ml, 15 mmol). After for 2 hours Tf_2O (1.1 ml, 3.9 mmol) was added and the solution was stirred at -78˚C for 5 hours. The solution was warmed up at room temperature and was diluted with anhydrous methanol. The oil was filtered through a pad of silica gel eluting with ether and concentrated to give yellow oil. Purification by column chromatography over silica gel gave the following compounds **190:** *E*-isomer (575 mg, 46%), Z-isomer (409 mg, 33%). ^{13}C NMR (75 MHz, CD_3OD) 8: 25.2, 25.3, 28.7, 33.7, 39.1,117.4,124.7,127.8,128.7, 129.0,129.5,130.6,131.0,137.8,161.9,170.1. MS (ESI) = 297 (MH^+).

Step 3: (*E*/*Z*)-Ethyl-3-methyl-8-acetoxy-8-(2-naphthyl)-2-octenoate (**191**)

[0400] An oven-dried flask equipped with a reflux condenser and a septum inlet was flushed with nitrogen and charged with a solution of 9-BBN (0.5M, 0.66 mmol) and then alkene **189** (168 mg, 0.66 mmol) at 0˚C. The mixture was warmed up slowly to room temperature and stirred for 6 hours. To this solution were added dioxane (4 ml), powder K_3PO_4 (191 mg, 0.90 mmol), $Pd(PPh_3)_4$ (18 mg, 0.015 mmol), and triflate **190** (solution in dioxane 0.18M, 3.42 ml, 0.60 mmol). The mixture was heated at 85˚C for 17 hours. Then the mixture was diluted with hexane at room temperature, and the residual borane was oxidized with 3 M NaOH (1 ml) and 30% H_2O_2 (1 ml) for 1 hour. The product was extracted, washed with brine, dried over Na_2SO_4, and finally isolated by chromatography over silica gel (hexanes:Et_2O: 10:1 to 1:1) to give 70% as mixture of *E* and *Z*-isomers **191** in a 1:1.1 ratio. The 20% of *Z*-isomer was isolated from the mixture: ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.1, 24.9, 25.5, 27.6, 32.9, 35.8, 50.6, 75.9, 115.6, 124.1, 125.5, 125.8, 126.0, 127.5, 127.8, 128.1, 328, 132.9, 137.9, 160.4, 166.5, 170.2. MS (ESI) = 375 (M^++Na).

Step 4: (*Z*)-8-Hydroxy-3-yl-methyl-8-(2-naphthyl)-2-octenoic acid (**192**)

[0401] Following a procedure described in Example 1, step 4, but substituting ester **191** for ester **3,** the compound **192** was obtained in 99% yield. ^{13}C NMR: (75 MHz, $CDCl_3$) δ 25.3, 26.9, 29.1, 34.0, 39.7, 75.1, 117.1, 125.3, 125.6, 126.5, 126.9, 128.5,128.8,128.9,134.3,134.7,143.9,162.2,169.7. MS (ESI) = 281 (MH^+-H_2O)

Step 5: (*Z*)-3-Methyl-7-(2-naphthoyl)-2-heptenoic acid (**193**)

[0402] To a solution of **192** (98 mg, 0.33 mmol) in dry dichloromethane (6 mL) was added a solution of Dess-Martin reagent (162 mg, 0.38 mmol) in dry dichloromethane (1 mL) *via cannula.* The mixture was stirred at room temperature for 24 hours. The mixture was diluted with ether and $NaHSO_3$ (221 mg) in aqueous solution was added with stirring until the phases are homogeneous. The product was extracted, washed with 5% $KHSO_4$, brine, dried over Na_2SO_4, and finally isolated by chromatography over silica gel (hexanes:Et_2O:. 4:1 to 1:1) to give **193** in 94% yield. ^{13}CNMR: (75 MHz, CD_3OD) δ: 25.2, 25.3, 28.7, 33.7, 39.1,117.4, 124.7,127.8,128.7,129.0,129.5,130.6,131.0,137.8,161.9,170.1. MS (ESI) = 297 (MH^+).

Step 6: (*Z*)-*N*-(2-Aminophenyl)-3-methyl-7-naphthoyl-2-heptenamide (**194**)

[0403] Following a procedure described in Example 35, but substituting respectively acid **193** for acid **80** and 1,2-

phenylenediamine for aniline, the compound **194** was obtained in 99% yield. ^{1}H NMR: (300 MHz, CD_3OD): 8.01 (d, 2H, J = 8.0 Hz), 7.92 (d, 2H, J = 8.8 Hz), 7.65-7.54 (m, 3H), 7.09 (d, J=8.0 Hz, 1H), 6.68 (dd, J = 7.7,7.4 Hz, 1H), 5.97 (s, 1H), 3.22 (t, J = 7.1 Hz, 2H), 2.82 (dd, J = 7.4, 7.7 Hz, 2H), 1.91-1.80 (m, 2H), 1.77-1.63 (m, 2H). ^{13}C NMR: (75 MHz, CH_3OD): 25.1, 25.2, 28.7, 33.4, 39.1, 118.6, 119.6, 124.7, 125.4, 126.9, 127.8, 127.9, 128.7, 129.4, 129.5, 130.7, 131.1, 133.9, 135.5, 136.9, 140.8, 143.0, 157.6, 167.5, 202.6

Example 118:

(*Z*)-*N*-(2-Aminophenyl)-3-methyl-7-(2-naphthoyl)heptanamide (198)

Step 1: Ethyl-3-methyl-8-8-O-acetoxy-8-(2-naphthyl)-2-octenoate (**195**)

[0404] To a cold (ice bath) solution of **191** (126 mg, 0.36 mmol) in dry CH_3OH (4 ml) were added 3 ml of a 4% CH_3OH solution of $NiCl_2.6H_2O$ (0.6 mmol). The solution was stirred for 30 min at 0˚C and then treated portionwise with $NaBH_4$ (46 mg,1.22 mmol). The resulting black solution was stirred for additional 1 hour at 0˚C, and then the ice bath was removed. After 18 hours at room temperature the mixture was treated with $NaHCO_3$, filtered through Celite, and concentrated. The residue was partitioned between saturated $NaHCO_3$ solution and dichloromethane. The combined organic layers were dried Na_2SO_4 and concentrated to give crude **195**. Flash chromatography on silica gel of the residue afforded 67% of **195** (86 mg). ^{13}C NMR (75 MHz, $CDCl_3$) δ:19.5, 25.5, 26.5, 30.1, 36.0, 36.4, 41.1, 41.4, 51.3, 76.1,124.2, 125.6,125.9,127.6,127.9,128.2,132.9,133.0, 137.9,170.3,173.6. MS (ESI) = 379 (M^++Na).

Step 2: 8-Hydroxx-methyl-8-(2-naphthyl)-octanoic acid (**196**)

[0405] Following a procedure described in Example 1, step 4, but substituting ester **195** for ester **3**, the compound **196** was obtained in 99% yield. ^{13}C NMR: (75 MHz, $CDCl_3$) δ: 20.0, 27.0, 27.9, 31.4, 37.6, 39.9, 42.6, 75.2,125.3,125.6,126.5,126.9, 128.6,128.8,128.9,134.3,134.7,143.9,177.2. MS (ESI) = 323 (M^++Na^+).

Step 3: 3-Methyl-7-naphthoyl-heptanoic acid (**197**)

[0406] Following a procedure described in Example 117, step 5, but substituting **196** for **192**, the compound **197** was obtained in 94% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.06-7.55 (m, 7H), 3.32 (br s, 1H), 3.16 (t, J = 6.9Hz, 1H), 2.32 (add, J = 6.0, 14.0 Hz,1H), 2.14-2.06 (m, 1H), 1.96-1.95 (m,1H), 1.78-1.73 (m, 2H), 1.47-1.29 (m, 3H), 0.97 (d, J = 6.04 Hz, 3H). MS (ESI) = 299 (MH^+).

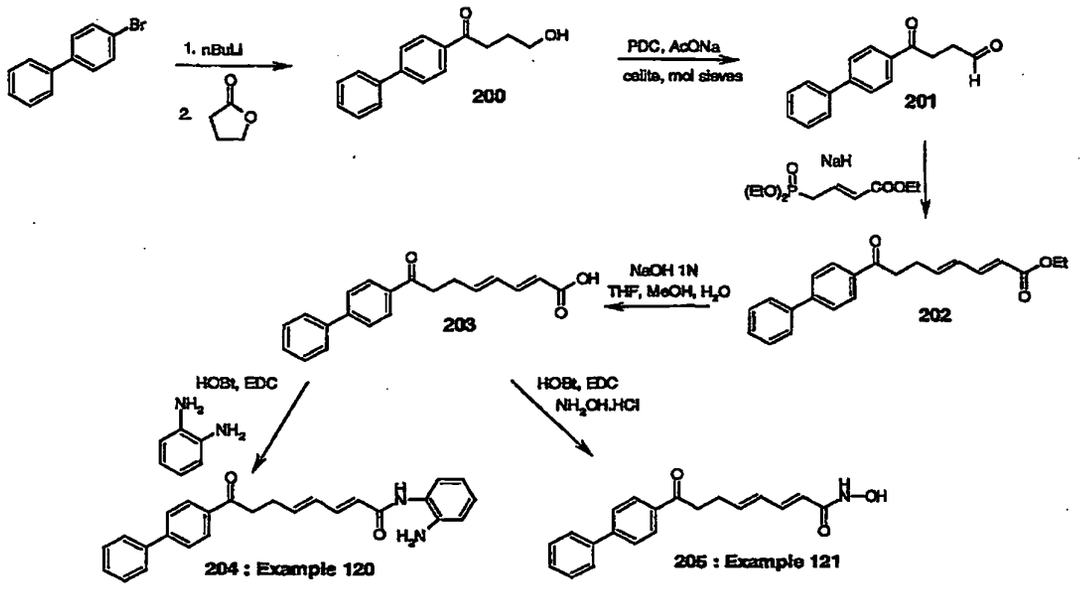
Step 4:*N*-(2-Aminophenyl)-3-Methyl-7-naphthoyl-heptanamide (**198**)

[0407] Following a procedure described in Example 35, but substituting acid **193** for acid 801,2-phenylenediamine for aniline, the compound 198 was obtained in 87% yield. ^{1}H NMR: (300 MHz, CD_3OD): 8.05-7.91 (m, 4H), 7.67-7.53 (m, 2H), 7.10-6.68 (m, 5H), 3.33-3.31 (m, 2H), 3.19 (dd, J = 6.9, 7.4 Hz, 2H), 2.47-1.29 (m, 7H), 1.05 (d, J = 6.6 Hz, 3H), ^{13}C NMR (75 MHz, CD_3OD): 20.1, 25.8, 27.7, 32.1, 37.7, 39.4, 44.87,118.6,119.5,124.7,127.1,127.8,128.3,128.8, 129.5,129.6,130.7,131.1,134.1, 137.1,174.6, 2027.

Example 119:

***N*-Hydroxy-3-methyl-7-(2-naphthoyl)heptanamide (199)**

[0408] Following a procedure analogous to that described in Example 14, step 3, but substituting carboxylic acid **197** for **37**, and using 1.1 equivalent of NH_2OH.HCl and triethylamine each, the title compound **199** was obtained in 63% yield. ^{1}H NMR: (300 MHz, CD_3OD): 8.07-7.58 (m, 7H), 3.32 (t, J = 1.7 Hz, 2H), 3.18 (dd, J= 7.4, 6.7 Hz, 2H), 2.13-1.30 (m, 7H), 0.95 (d, J = 6.3 Hz, 3H). "C NMR (75 MHz, CD_3OD):19.7, 25.7, 27.6, 31.7, 37.6, 39.4, 41.4,124.7,127.9,128.7, 129.4,129.6, 130.7,131.1,134.1,135.6,137.1,172.4, 2028.



[0409] Examples 120 and 121 are for illustration purpose only.

Example 120:

(*E*,*E*)-*N*-(2-Aminophenyl)-7-[(4-biphenyl)carbonyl]-2,4-heptadienamide (204)

Step 1: 1-(4-Biphenyl)-4-hydroxybutanone (**200**)

[0410] To a solution of bromobiphenyl (1 g, 4.3 mmol) in THF (20 mL) stirred at - 78˚C under nitrogen was dropwise added n-BuLi (2.5M in hexane, 1.89 mL, 4.72 mmol). The mixture was stirred for 2 hours at - 78˚C, then warmed up to 0˚C and transferred via cannula over a solution of γ-butyrolactone (362 μL, 4.72 mmol) in THF (10 mL) cooled at -78˚C. The reaction mixture was stirred for 2 hours at - 78˚C, quenched by a slow addition of water (10 mL), and then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by flash silica gel chromatography (40% ethyl acetate in hexane) afforded the corresponding the alcohol **200** (430 mg, 42% yield). MS (ESI) = 241 (MH^+).

Step 2: 3-[(4-Biphenyl)carbonyl]propionaldehyde (**201**)

[0411] To a suspension of pyridinium chlorochromate (448 mg, 2.08 mmol), sodium acetate (170 mg, 2.08 mmol), Celite (200 mg) and molecular sieves 4Å (10 mg) in anhydrous dichloromethane (10 mL) at room temperature under nitrogen was slowly added a solution of alcohol **200** in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 30 minutes and then filtered through a short pad of Celite. The organic layer was dried ($MgSO_4$), concentrated, and the crude was purified by flash silica gel chromatography (40% ethyl acetate in hexane) affording the aldehyde **201** (160 mg, 73% yield). MS (ESI) = 239 (MH^+).

Step 3: (*E*,*E*)-Ethyl-7-[(4-biphenyl)carbonyl]-2,4-heptadienoate (**202**)

[0412] To a solution of aldehyde **201** (180mg, 0.75 mmol) in THF (10 mL), stirred at 0˚C under nitrogen, was added triethyl-4-phosphonocrotonate (220 μL, 0.98 mmol) followed by sodium hydride (40 mg, 0.98 mmol). The mixture was allowed to warm up to room temperature in 2 hours and then quenched by adding water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash silica gel chromatography (30% ethyl acetate in hexane) afforded the corresponding diene 202 (100 mg, 40% yield). MS (ESI) = 335 (MH^+).

Step 4: (*E*,*E*)-7-[(4-Biphenyl)carbonyl]-2,4-heptadienoic acid (**203**)

[0413] Following the procedure described in Example 18, step 3, but substituting ester **202** for ester **49a**, the title

compound **203** was obtained in 80% yield. ^{1}H NMR: (300 MHz, $CDCl_3$:CD_3OD 5:1) δ: 7.89-7.95 (2 m, 2 H), 7.49-7.65 (m, 4 H), 7.28-7.40 (m, 3 H), 7.15 (dd, J =15.3 , 9.9 Hz, 1H), 6.05-6.24 (m, 2 H), 5.69 (d, J = 15.6 Hz, 1H), 3.1 (t, J = 7.2 Hz, 2 H), 2.50-2.60 (m, 2H).

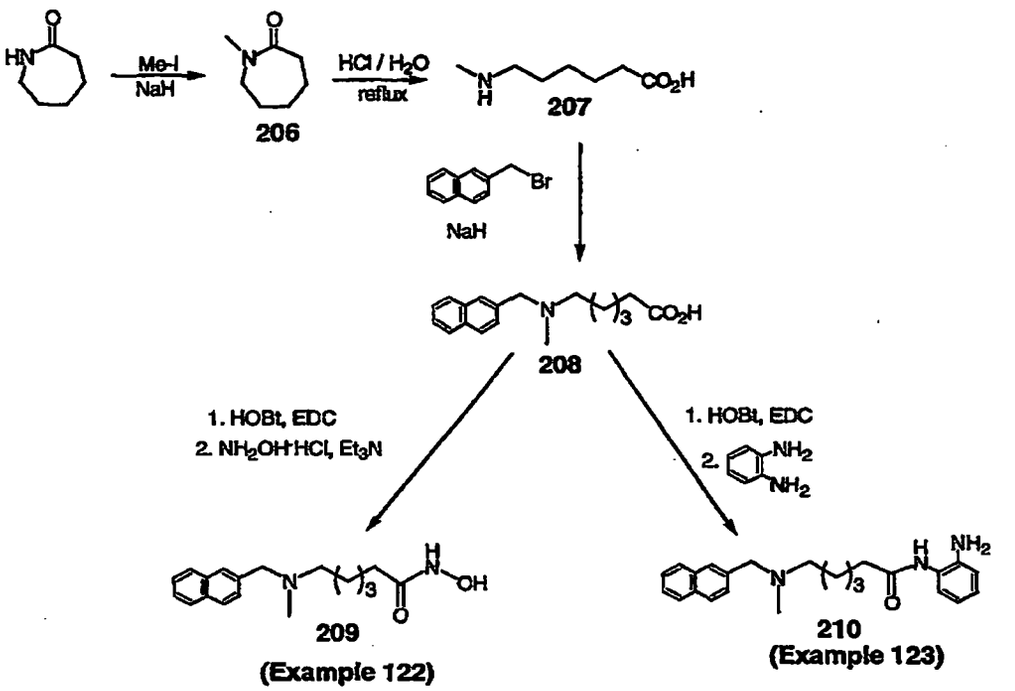
Step 5: (*E*,*E*)-*N*-(2-Aminophenyl)-7-[(4-biphenyl)carbonyl]-2,4-heptadienamide (**204**)

[0414] Following the procedure described in Example 22, but substituting carboxylic acid **203** for **50g**, the title compound **204** was obtained in 47% yield. MS (ESI) = 397 (MH^-).

Example 121:

(*E*,*E*)-*N*-Hydroxy-7-[(4-biphenyl)carbonyl]-2,4-heptadienamide (205)

[0415] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **203** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **205** was obtained in 35% yield. MS (ESI) = 322 (MH^+).



[0416] Examples 122 and 123 are for illustration purpose only.

Example 122:

***N*-Hydroxy-*N*-(2-naphthylmethyl-methylamino)hexanamide (209)**

Step 1: *N*-Methyl-ε-caprolactam (**206**)

[0417] To a solution of ε-caprolactam (20 g, 17.6 mmol) in anhydrous THF (15 mL) at 0˚C was added NaH, 60% dispersion in oil (1.06 g, 26.0 mmol), and the mixture was stirred at 0˚C for 30 minutes. The cold bath was removed and the mixture was stirred at room temperature for 1 hour and then cooled again to 0˚C Methyl iodide (1.65 mL, 26.0 mmol) was added dropwise over 10 minutes, then the cold bath was removed and the mixture was stirred at room temperature for 18 hours. The excess NaH was quenched with methanol, THF was removed in *vacuo* and the crude was partitioned between ethyl acetate and water. The aqueous phase was washed with ethyl acetate (2 x 30 mL), adding solid NaCl to break the emulsion. Organic washing were combined and dried over Na_2SO_4. Ethyl acetate was removed in *vacuo* and the crude product **206** (1.54 g, 68%) was used without further purification. MS (ESI) = 128 (MH^+).

Step 2: 6-*N*-Methylamino hexanoic acid (**207**)

[0418] A mixture of *N*-methyl ε-caprolactam **206** (1.1 g, 8.6 mmol) and 8N HCl (8 mL) and H_2O (4 mL) was refluxed for 18 hours. The resulting solution was cooled to room temperature, diluted with H_2O (20 mL) and the mixture was evaporated to dryness. Additional H_2O (10 mL) was added and again removed in *vacuo.* The crude residue was triturated with acetone (2X 5 mL), removing acetone each time. The resulting solid was dried in *vacuo* to yield the desired product **207** (1.21 g, 96%). MS (ESI) =146 (MH^+).

Step 3: 6-*N*-(2-naphthylmethyl-methylamino)hexanoic acid (**208**)

[0419] Following the procedure described in Example 122, step 1, but substituting respectively the amino acid **207** for the azepan-2-one, 2-bromomethylnaphthalene for methyl iodide, and DMF for THF, the title compound 208 was obtained in 45% yield after purification by column chromatography (33% to 90% methanol in dichloromethane).

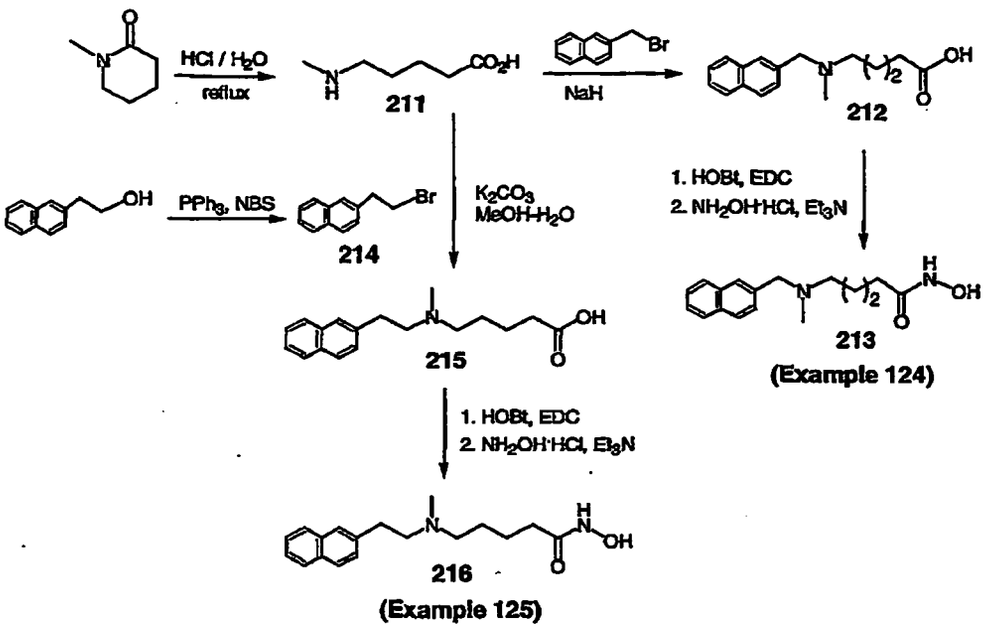
Step 4: *N*-Hydroxy-6-*N*-(2-naphthylmethyl-methylamino)hexanamide (**209**)

[0420] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **208** for **37**, and using 1.1 equivalent of $NH_2OH{\cdot}HCl$ and triethylamine each, the title compound **209** was obtained in 20% yield. ^1H NMR: (300 MHz, DMSO-d_6) δ 10.3 (br s, 1H), 8.65 (br d, J = 0.8 Hz, 1H), 7.86 (m, 3H), 7.80 (s,1H), 7.47 (m, 3H), 3.58 (s, 2H), 2.33 (t, J = 7.2 Hz, 2H), 2.12.(s, 3H), 1.93 (t, J = 7.3 Hz, 2H), 1.48 (m, 4H),1.26 (m, 2H).

Example 123:

***N*-(2-Aminophenyl)-*N*-(2-naphthylmethyl-methylamino)hexanamide (210)**

[0421] Following the procedure described in Example 22, but substituting carboxylic acid **208** for **50g**, the title compound **210** was obtained in 20% yield. ^1H NMR: (300 MHz, DMSO-d_6) δ 9.1 (br s, 1H), 7.86 (m, 3H), 7.86 (m, 3H), 7.78 (br s, 1H), 7.47 (m, 3H), 7.14 (dd, J = 8.0,1.4 Hz, 1H), 6.87 (dt, J = 8.0,1.4 Hz, 1H), 6.70 (dd, J = 8.0,1.4 Hz, 1H), 6.51 (dt, J = 7.4,1.4 Hz, 1H), 4.81 (br, 2H), 3.63 (br, 2H), 2.39 (br, 2H), 2.30 (t, J = 7.3 Hz, 2H), 2.16 (br s, 3H), 1.56 (m, 4H), 1.35 (m, 2H).



[0422] Examples 124 and 125 are for illustration purpose only.

Example 124:

***N*-Hydroxy-5-*N*-(2-naphthylmethyl-methylamino)pentanamide (213)**

Step 1: 5-Methylamino-pentanoic acid (**211**)

[0423] Following the procedure described in Example 122, step 2, but substituting 1-methyl-2-pipendone for **206,** the title compound **211** was obtained in 95% yield. MS (ESI) = 132 (MH^+).

Step 2: 5-*N*-(2-naphthylmethyl-methylamino)pentanoic acid (**212**)

[0424] Following the procedure described in Example 122, step 3, but substituting amino acid **211** for **207**, the title compound **212** was obtained in 58% yield. MS (ESI) = 272 (MH^+).

Step 3: *N*-Hydroxy-5-*N*-(2-naphthydmethyl-methylamino)pentanamide (**213**)

[0425] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **212** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **213** was obtained in 33% yield. ^1H NMR: (300 MHz, DMSO-d_6) δ 10.30 (br s, 1H), 8.61 (br s, 1H), 7.85 (m, 3H), 7.75 (s, 1H), 7.46 (m, 3H), 3.57 (s, 2H), 2.34 (t, J = 6.9 Hz, 2H), 2.1 (s, 3H), 1.93 (t, J = 6.9 Hz, 2H), 1.47 (m, 4H).

Example 125:

***N*-Hydroxy-5-*N*-[2-(2-naphthylethyl)-methylamino]pentanamide (216)**

Step 1: 2-(2-Bromoethyl)naphthalene (**214**)

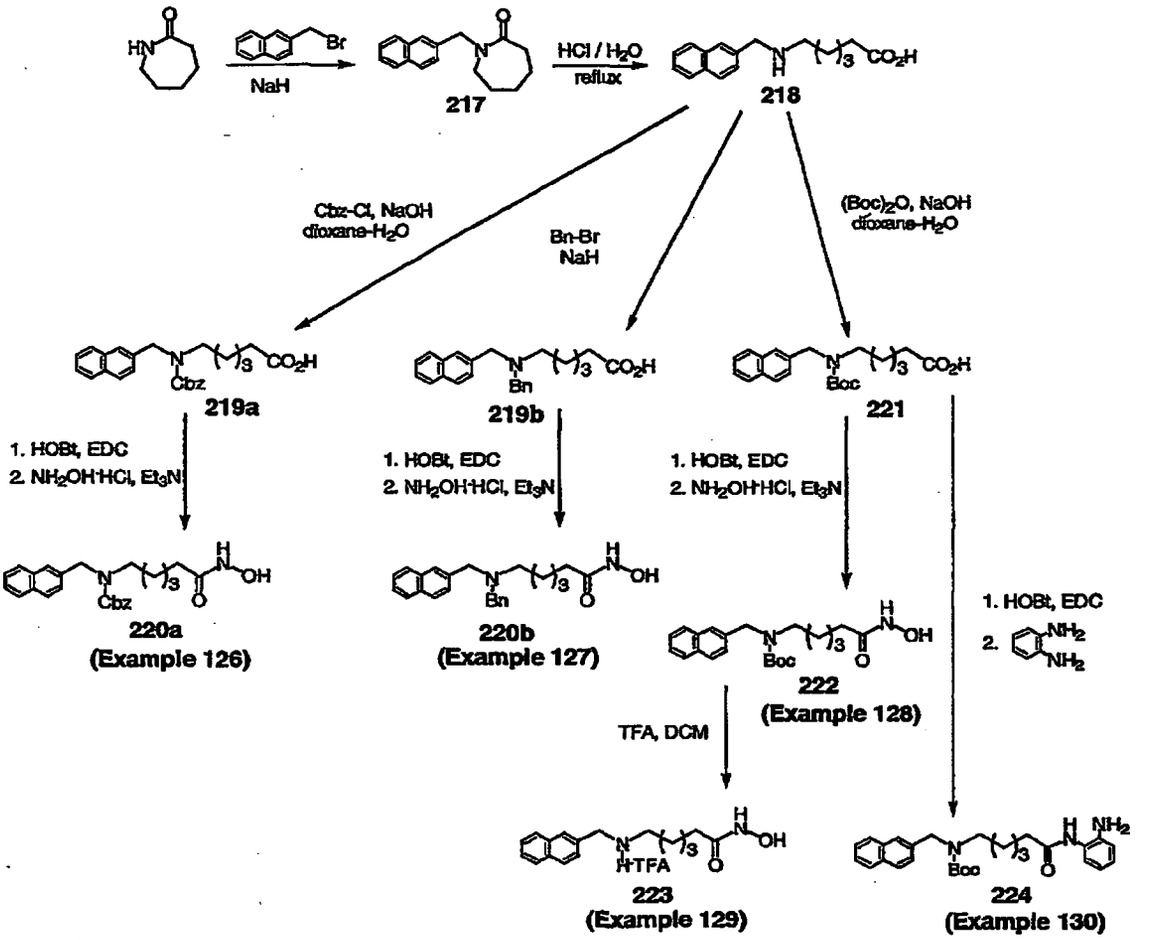
[0426] A solution of triphenylphosphine (0.57 g, 2.2 mmol) and *N*-bromosuccinimide (0.39 g, 2.2 mmol) in anhydrous dichloromethane (4 mL) was stirred for 10 minutes. 2-Naphthalenethanol (0.25 g,1.45 mmol) was added, followed immediately by imidazole (0.25 g,1.45 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was partitioned between H_2O and dichloromethane. The aqueous layer was extracted with diethyl ether (2 x 20 mL) and the combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The crude residue was purified by column chromatography through a plug of silica gel eluting with 10% ethyl acetate in hexanes to afford a colorless solid **214** (0.29 g, 86%).

Step 2: 5-*N*-[2-(2-Naphthylethyl)-methylamino]pentanoic acid (**215**)

[0427] A mixture of amino acid **211** (60 mg, 0.45 mmol), 2-(2-bromoethyl)naphthalene (0.15 g, 0.64 mmol) and potassium carbonate (0.24 g, 1.7 mmol) in methanol-H_2O (2 :1.5 mL) was heated at reflux for 7 hours and then at room temperature for 18 hours. Methanol was removed in *vacuo,* the remaining aqueous residue was partitioned between ethyl acetate and H_2O and extracted with ethyl acetate (2 x 20 mL). The aqueous layer was evaporated to dryness, triturated with methanol and filtered to remove inorganic solids. The filtrate was evaporated to dryness and then purified by column chromatography using a gradient of 25 to 75% methanol in dichloromethane to afford a colorless solid **215** (85 mg, 69%). MS (ESI) = 286 (M+1).

Step 3:*N*-Hydroxy-5-*N*-[2-(2-naphthylethyl)-methylamino]pentanamide (**216**)

[0428] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **215** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **216** was obtained in 15% yield. ^1H NMR: (300 MHz, DMSO-d_6) δ 7.83 (m, 3H), 7.71 (s, 1H), 7.44 (m, 3H), 286 (dd, J = 8.5, 6.9 Hz, 2H), 2.60 (m, 2H), 2.34 (t, J = 7.0 Hz, 2H), 2.2 (s, 3H), 1.93 (t, J = 7.15 Hz, 2H), 1.43 (m, 4H).



[0429] Examples 126 to 130 are for illustration purpose only.

Example 126:

***N*-Hydroxy-6-*N*-(Benzyloxycarbonyl-2-naphthylmethylamino)hexanamide (220a)**

Step 1: *N*-2-Naphthylmethyl-e-caprolactam (**217**)

[0430] Following the procedure described in Example 122, step 1, but substituting respectively 2-bromomethylnaphthalene for methyl iodide, and DMF for THF, the title compound **217** was obtained in 97% yield. MS (ESI) = 254 (MH^+).

Step 2: 6-*N*-(2-Naphthylmethylamino)hexanoic acid (**218**)

[0431] Following the procedure described in Example 122, step 2, but substituting **217** for 206, the title compound **218** was obtained in 69% yield. MS (ESI) = 272 (MH^+).

Step 3: 6-*N*-(Benzyloxycarbonyl-2-naphthylamino)hexanoic acid (**219a**)

[0432] To an emulsion of compound **218** (70 mg, 0.26 mmol) in dioxane-H_2O (1.5 : 2.5 mL) stirring at room temperature was added NaOH (0.1 g, 2.5 mmol) dissolved in 1 mL H_2O followed by benzyloxycarbonyl chloride (0.044 mL, 0.31 mmol). The mixture was stirred vigorously for 18 hours. Dioxane was removed in *vacuo* and the resulting aqueous layer was diluted with H_2O and extracted with diethyl ether (2 x 20mL). Subsequently, the aqueous layer was neutralized to pH 7 using a $KHSO_4$ solution (0.37 M) and then extracted with ethyl acetate (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4 and then evaporated to dryness to afford a crude oil **219a** (75 mg, 72%) that was used without further purification. MS (ESI) = 428 (MH^+).

Step 4: *N*-Hydroxy-6-*N*-(Benzyloxycarbonyl-2-naphthylmethylamino)hexanamide (**220a**)

[0433] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **219a** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **220a** was obtained in 66% yield. ^1H NMR-(300 MHz, DMSO-d_6) δ 10.30 (br s,1H), 8.65 (br s, 1H), 7.87 (m, 3H), 7.7 (br d, J = 10.7 Hz, 1H), 7.49 (t, J = 3.7 Hz, 2H), 7.38 (m, 4H), 7.25 (m, 2H), 5.13 (br d, J = 6.6 Hz, 2H), 4.61 (s, 2H), 3.22 (m, 2H), 2.1 (m, 1H), 1.88 (m, 2H), 1.47 (m, 4H), 1.20 (m, 2H).

Example 127:

***N*-Hydroxy-6-*N*-(Benzyl-2-naphthylmethylamino)hexanamide (220b)**

Step 1: 6-*N*-(Benzyl-2-naphthylmethylamino)hexanoic acid (**219b**)

[0434] Following the procedure described in Example 122, step 1, but substituting respectively the amino acid **218** for the ε-caprolactam, benzyl bromide for methyl iodide, and DMF for THF, the title compound **219b** was obtained in 56% yield. MS (ESI) = 362 (MH^+).

Step 2: *N*-Hydroxy-6-*N*-(benzyl-2-naphthylmethylamino)hexanamide (220b)

[0435] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **219b** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **220b** was obtained in 27% yield. ^1H NMR (300 MHz, DMSO-d_6) δ 10.29 (br s, 1H), 8.65 (br s, 1H), 7.84 (m, 4H), 7.48 (m, 3H), 7.33 (m, 4H), 7.21 (m, 1H), 3.66 (s, 2H), 3.54 (s, 2H), 3.35 (t, J = 7.1 Hz, 2H),1.87 (t, J = 7.3 Hz, 2H), 1.46 (m, 2H), 1.40 (m, 2H), 1.19 (m, 2H).

Example 128:

***N*-Hydroxy-6-*N*-(*tert*-butoxycarbonyl-2-naphthylmethylamino)hexanamide (222)**

Step 1: 6-*N*-(*tert*-Butoxycarbonyl-2-naphthylmethylamino)hexanoic acid (**221**)

[0436] Following the procedure described in Example 126, step 3, but substituting di-*tert*-butyl dicarbonate for benzyloxycarbonyl chloride, the title compound **221** was obtained in 88% yield. MS (ESI)= 394 (MH^+).

Step 2: *N*-Hydroxy-6-*N*-(*tert*-butoxycarbonyl-2-naphthylmethylamino)hexanamide (**222**)

[0437] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **221** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **222** was obtained in 60% yield. ^1H NMR: (300 MHz, DMSO-D_6) δ 10.31 (br s, 1H), 8.65 (br s, 1H), 7.87 (m, 3H), 7.7 (br s, 1H), 7.5 (m, 2H), 7.37 (m, 1), 4.52 (br s, 2H), 3.15 (m, 2H), 1.90 (t, J = 7.3 Hz, 2H), 1.41 (m, 13H), 1.17 (m, 2H).

Example 129:

***N*-Hydroxy-6-*N*-(2-naphthylmethylamano)hexanamide trifluoroacetate (223)**

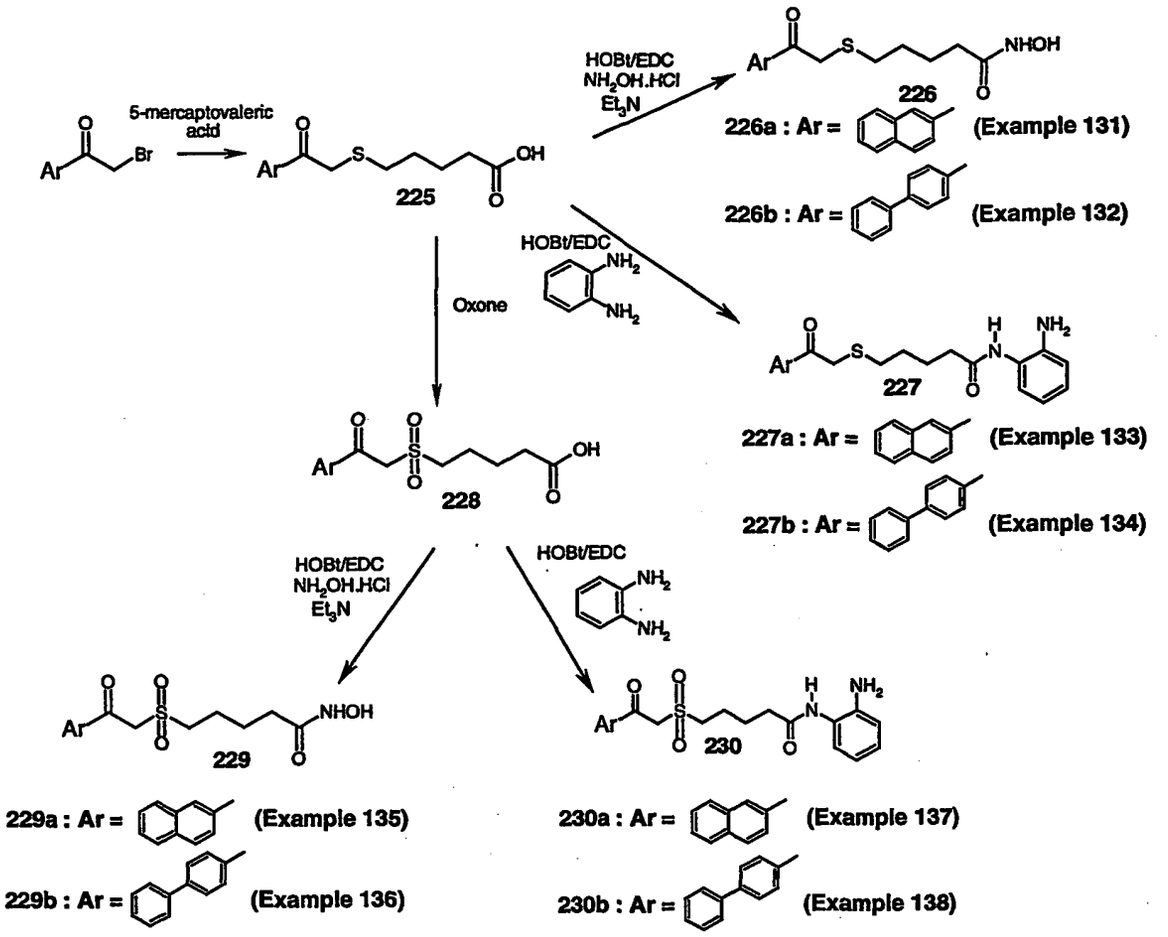
[0438] To a stirring solution of compound **222** (65.0 mg, 0.17 mmol) in anhydrous dichloromethane (3 mL) at room temperature was added trifluoroacetic acid (3.5 mL) dropwise. The solution was stirred for 18 hours. dichloromethane and trifluoroacetic acid were removed in *vacuo,* the residue was dissolved in H_2O and then extracted with ethyl acetate (2 x 20 mL). The aqueous layer was lyophilized to yield the final product **223** as a colorless oil (30.0 mg, 45%). ^1H NMR : (300 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.79 (br s, 2H), 8.67 (s, 1H), 7.96 (m, 4H), 7.58 (m, 3H), 4.3 (br s, 2H), 2.94 (br s, 2H), 1.93 (t, J = 7.4 Hz, 2H), 1.61 (m, 2H), 1.49 (m, 2H), 1.27 (m, 2H).

Example 130:

***N*-(2-Aminophenyl)-6-*N*-(*tert*-butoxycarbonyl-2-naphthylmethylamino)-hexanamide (224)**

[0439] Following the procedure described in Example 22, but substituting carboxylic acid **221** for **50g**, the title compound **224** was obtained in 53% yield. ^1H NMR: (300 MHz, DMSD-d_6) δ 9.06 (br s, 1H), 7.87 (m, 3H), 7.71(br s, 1H),

7.49 (m, 2H), 7.38 (d, J = 8.5 Hz, 1H), 7.13 (d, J = 6.6 Hz, 1H), 6.88 (m, 1H), 6.70 (dd, J = 1.1, 8.0 Hz, 1H), 6.52 (dt, J = 1.4,8.2 Hz, 1H), 4.8 (m, 2H), 4.54 (br s, 2H), 3.17 (m, 2H), 2.28 (t, J = 7.3 Hz, 2H), 1.44 (m, 15H).



Example 131:

***N*-Hydroxy-5-(2-naphthoylmethylsulfanyl)pentanamide (226a)**

Step 1: 5-(2-Naphthoylmethylsulfanyl)pentanoic acid (**225a**)

[0440] To a solution of bromomethyl-2-naphthyl ketone (2 g, 8.00 mmol) in anhydrous THF (50 mL) was added 5-mercaptovaleric acid (1.07 g, 8.00 mmol), followed by potassium carbonate (5.71 g, 41 mmol). The suspension was refluxed for 1 hour, cooled to the room temperature and filtered. The solid was collected, dissolved in a 1:1 mixture water-THF and acidified with HCl (pH 1-2). The acidic solution was extracted with ether, dried ($MgSO_4$), filtered and evaporated to produce the title compound **225a** (1.21 g, 50% yield) ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.98 (br s,1H), 8.69 (s, 1H), 8.10 (d, J = 7.5 Hz, 1H), 8.00-7.98 (m, 3H), 7.67-7.61 (m, 2H), 4.09 (s, 2H), 2.52 (t, J = 6.6 Hz, 2H), 2.19 (t, J = 6.6 Hz, 2H), 1.56-1.53 (m, 4H).

Step 2: *N*-Hydroxy 5-(2-naphthoymethylsulfanyl)pentanamide (**226a**)

[0441] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **225a** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **226a** was obtained in 24% yield. 1H NMR: (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.70 (s, 1H), 8.66 (s, 1H), 8.10 (d, J = 7.7 Hz, 1H), 8.00-7.97 (m, 3H), 7.70-7.59 (m, 2H), 2.51 (t, J = 6.9 Hz, 2H), 4.10 (s, 2H), 1.94-1.91 (m, 2H),1.53-1.51 (m, 4H).

Example 132:

***N*-Hydroxy-5-(4-biphenylcarbonylmethanesulfanyl)pentanamide (226b)**

Step 1: 5-(4-Biphenylcarbonylmethanesulfanyl)pentanoic acid (**225b**)

[0442] Following the procedure described in Example 131, step 1, but substituting bromomethyl-4-biphenyl ketone for bromomethyl-2-naphthyl ketone, the title compound **225b** was obtained in 81% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 2H), 7.71-7.62 (m, 4H), 7.50-7.40 (m, 3H), 3.81 (s, 2H), 2.60 (t, J = 6.3 Hz, 2H), 2.38 (t; J = 6.9 Hz, 2H),1.72-1.68 (m, 4H).

Step 2: *N*-Hydroxy-5-(4-biphenylcarbonylmethanesulfanyl)pentanamide (**226b**)

[0443] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **225b** for **37**, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **226b** was obtained in 30% yield. ^{1}H NMR. (300 MHz, DMSO-d_6) δ 10.31 (s,1H), 8.65 (s,1H), 8.05 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.51-7.41 (m, 3H), 3.98 (s, 2H),1.92 (br s, 4H),1.51 (br. s, 4H),

Example 133:

***N*-(2-Aminophenyl)-5-(2-naphthoylmethylsulfanyl)pentanamide (227a)**

[0444] Following the procedure described in Example 22, but substituting carboxylic acid **225a** for **50g**, the title compound **227a** was obtained in 20% yield. ^{1}H NMR: (300 MHz, DMSO-d_6) δ 9.07 (s,1H), 8.69 (s, 1H), 8.10-7.97 (m, 4H), 7.68-7.58 (m, 2H), 7.11 (d, J = 7.1 Hz, 1H), 6.86 (t, J = 7.1 Hz, 1H), 6.80 (d, J = 7.7 Hz, 1H), 6.50 (t, J = 7.4 Hz, 1H), 4.78 (s, 2H), 4.10 (s, 2H), 2.56 (t, J = 6.6 Hz, 2H), 230 (t, J = 6.6 Hz, 2H),1.61 (br s, 4H).

Example 134:

***N*-(2-Aminophenyl)-5-(4-biphenylcarbonylmethanesulfanyl)pentanamide (227b)**

[0445] Following the procedure described in Example 22, but substituting carboxylic acid **225b** for **50g,** the title compound **227b** was obtained in 34% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.09 (s,1H), 8.05 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 7.7 Hz, 2H), 7.51-7.41 (m, 3H), 7.12 (d, J = 7.5 Hz, 1H), 6.86 (t, J = 7.5 Hz,1H), 6.69 (d, J = 7.8 Hz,1H), 6.51 (t, J = 7.5 Hz,1H), 4.79 (s, 2H), 4.00 (s, 2H), 2.53 (t, J = 6.6 Hz, 2H), 2.30 (t, J = 7.2 Hz, 2H), 1.61 (br s, 4H).

Example 135:

***N*-Hydroxy-5-(2-naphthoylmethylsulfonyl)pentanamide (229a)**

Step 1: 5-(2-Naphthxoylmethylsulfonyl)pentanoic acid (**228a**)

[0446] To a solution of **225a** (755 mg, 2.50 mmol) in methanol (30 mL) at 0˚C was added a solution of oxone (2.3 g, 3.75 mmol) in water (30 mL). The mixture stirred at the same conditions for 6 hours, methanol was removed in vacuum and the water phase was extracted with chloroform. The extract was dried over $MgSO_4$, filtered and evaporated to afford the title compound **228a** (520 mg, 62% yield). MS (ESI) = 335 (MH^+).

Step 2: *N*-Hydroxy-5-(2-naphthoylmemylsulfonyl)pentanamide (**229a**)

[0447] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **228a** for **37,** and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **229a** was obtained in 30% yield. ^{1}H NMR: (300 MHz, DMSO-d_6) δ 10.38 (br s,1H), 8.83 (s,1H), 8.71 (s,1H), 8.13 (d, J = 7.7 Hz, 1H), 8.06-7.99 (m, 3H), 7.74-7.63 (m, 2H), 5.19 (s,1H), 3.34 (t, J = 7.4 Hz, 2H), 2.00 (t, J = 6.7 Hz, 2H), 1.78-1.60 (m, 4H).

Example 136:

***N*-Hydroxy-5-(4-biphenylcarbonylmethylsulfonyl)pentanamide (229b)**

Step 1: 5-(4-Biphenylcarbonylmethanesulfonyl)pentanoic acid (**228b**)

[0448] Following the procedure described in Example 135, step 1, but substituting **228b** for **228a,** the title compound **228b** was obtained in 91% yield.

Step 2: *N*-Hydroxy-5-(4-biphenylcarbonylmethylsulfonyl)pentanamide (**229b**)

[0449] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **228b** for **37,** and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound **228b** was obtained in 52% yield. ^1H NMR: (300 MHz, DMSO-d_6) δ 10.37 (s,1H), 8.70 (s, 1H), 8.11 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 7.77 (dd, J =1.4 Hz, J = 8.5 Hz, 2H), 7.53-7.43 (m, 3H), 5.08 (s, 2H), 3.38-3.25 (t, 2H), 1.99 (t, J = 6.6 Hz, 2H), 1.72-1.61 (m, 4H).

Example 137:

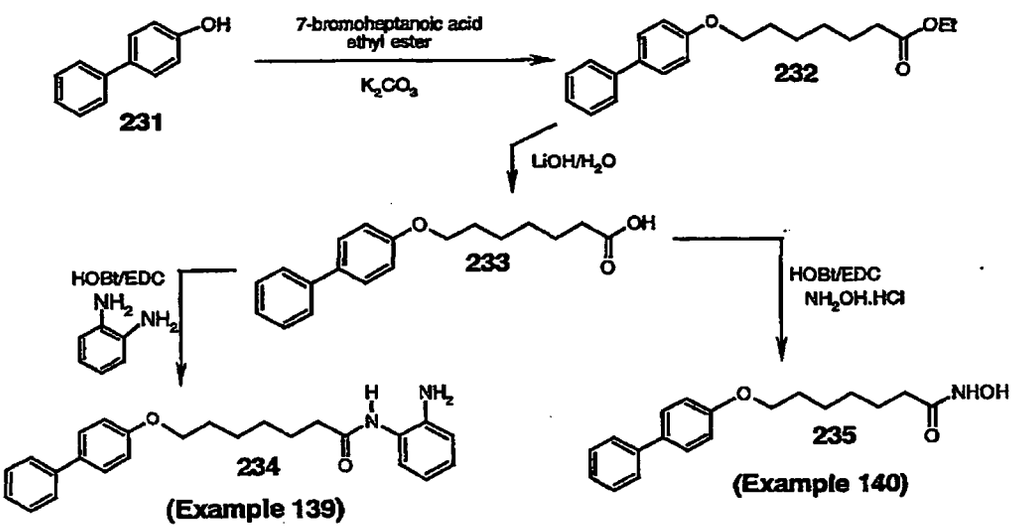
***N*-(2-Aminophenyl)-5-(2-naphthoylmethylsulfonyl)pentanamide (230a)**

[0450] Following the procedure described in Example 22, but substituting carboxylic acid **228a** for **50g,** the title compound **230a** was obtained in 30% yield. ^1H NMR (300 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.83 (s, 1H), 8.12 (d, J = 7.4 Hz, 1H), 8.06-7.99 (m, 3H), 7.74-7.63 (m, 2H), 7.15 (dd, j = 1.4 Hz, J = 8.0 Hz, 1H), 6.88 (dd, J = 1.4 Hz, 8.0 Hz, 1H), 6.70 (dd, J = 1.4 Hz, 8.0 Hz, 1H), 6.52 (dd, J = 1.2 Hz, 8.8 Hz, 1H), 5.21 (s, 1H), 4.82 (br s, 2H), 3.38 (t, J = 7.1 Hz, 2H), 2.38 (t, J = 7.1 Hz, 2H), 1.84-1.72 (m, 4H).

Example 138:

***N*-(2-Aminophenyl)-5-(4-biphenylcarbonylmethylsulfon yl)pentanamide (229b)**

[0451] Following the procedure described in Example 22, but substituting carboxylic acid **228b** for **50g,** the title compound **230b** was obtained in 52% yield.
^1H NMR: (300 MHz, (MSO-d_6) δ 9.12 (s,1H), 8.13 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 82 Hz, 2H), 7.77 (d, J = 6.7 Hz, 2H), 7.53-7.44 (m, 3H), 7.15 (d, J = 8.0 Hz,1H), 6.88 (t, J = 8.0 Hz, 1H), 6.70 (d J = 8.0 Hz, 1H), 6.52 (t, J = 7.7 Hz, 1H), 5.11 (s, 2H), 4.82 (s, 2H), 3.36 (t, J = 6.9 Hz, 2H), 237 (t, J = 7.1 Hz, 2H), 1.78-1.71 (m, 4H).



[0452] Examples 139 and 140 are for illustration purpose only.

Example 139:

***N*-(2-Aminophenyl)-7-(4-biphenyloxy)heptanamide (234)**

Step 1: Eexyl-7-(biphenyloxy)heptanoate (**232**)

[0453] To a solution of 4-phenylphenol (**231**) (1.00 g, 5.88 mmol) in acetone (100 mL) was added potassium carbonate (3.25 g, 23.52 mmol) and potassium iodide (200 mg,1.57 mmol), followed by the addition of ethyl-7-bromoheptanoate (1.81 g, 7.65 mmol). The suspension was refluxed for 36 hours, cooled to room temperature and filtered. Filtrate was evaporated and the remained solid was recrystallized from hexane to produce the title compound **232** (1.73 g, 90% yield). MS(ESI)=327(MH^+).

Step 2: 7-(4-Biphenyloxy)heptanoic acid (**233**)

[0454] To a solution of the ester **232** (1.70 g, 5.21 mmol) in THF (50 mL) was added a solution of lithium hydroxide hydrate (1.30 g, 30.95 mmol) in water (50 mL). The reaction mixture was stirred 18 hours at room temperature, THF was evaporated and the aqueous phase was acidified with conc. HCl (pH 1-2). A precipitate formed which was collected by filtration and dried to afford the title compound 233 (1.54 g, 99%). MS (ESI) = 321 (M^++Na).

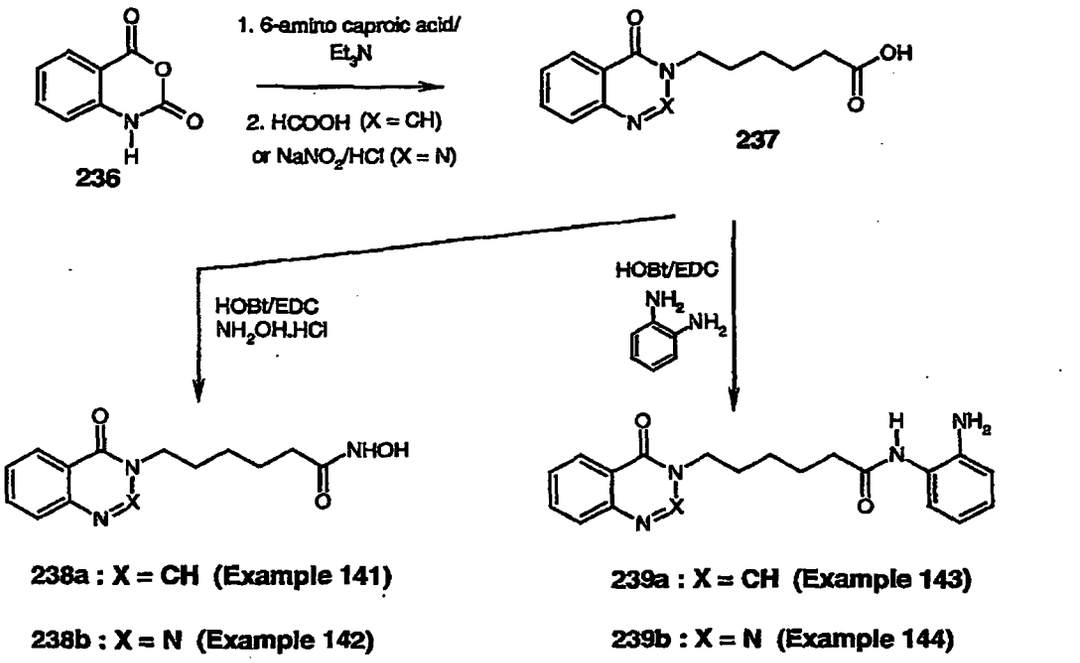
Step 3: *N*-(2-Aminophenyl)-7-(4-biphenyloxy)heptanamide (**234**)

[0455] Following the procedure described in Example 22, but substituting carboxylic acid 233 for 50g, the title compound **234** was obtained in 44% yield.^{1}H NMR: (300 MHz, DMSO-d_6) δ 9.08 (s, 1H), 7.60-7.55 (m, 4H), 7.41 (t, J = 7.7 Hz, 2H), 7.29 (t, J = 7.1 Hz, 1H), 7.14 (dd, J = 8.0,1.4 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.87 (t, J = 8.0 Hz, 1H) 6.70 (dd, J = 8.0,1.4 Hz, 1H), 6.52 (dd, J = 8.5, 1.1 Hz, 1H), 4.81 (br s, 2H), 4.00 (t, J = 6.3 Hz, 2H), 2.32 (t, J = 7.4 Hz, 2H), 1.76-1.69 (m, 2H), 1.67-1.57 (m, 2H), 1.47-1.38 (m, 4H).

Example 140:

***N*-Hydroxy-7-(4-biphenyloxy)heptanamide (235)**

[0456] Following the procedure described in Example 14, step 3, but substituting carboxylic acid **233** for **37**, and using 1.1 equivalent of NH_2OH.HCl and triethylamine each, the title compound **235** was obtained in 52% yield. ^{1}H NMR: (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.65 (s, 1H), 7.60-7.54 (m, 4H), 7.40 (t, J = 7.5 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 6.98 (d, J = 8.7 Hz, 2H), 3.97 (t, J = 6.3 Hz, 2H), 1.93 (t, J = 7.1 Hz, 2H), 1.70 (t, J = 7.4 Hz, 2H), 1.52-1.28 (m, 6H).



[0457] Examples 141 to 144 are for illustration purpose only.

Example 141:

***N*-Hydroxy-6-[3-(4-Oxo-4*H*-quinazolinyl)]hexanamide (238a)**

Step 1: 6-[3-(4-Oxo-4*H*-quinazolinyl)]hexanoic acid (**237a**)

[0458] To a solution of 6-aminohexanoic acid (2.88 g, 20.00 mmol) in water (50 mL) was added triethylamine (3.06 ml, 22.00 mmol) followed by a portionwise addition of 1*H*-benzo[d][1,3]oxazine-2,4-dione (isatoic anhydride, **236**) (3.26 g, 20.00 mmol). The reaction mixture was stirred for 2 hours at 30-40˚C, cooled to room temperature and evaporated in vacuum to form an oily residue. This material was refluxed for 7 hours in formic acid (70 ml), cooled to room temperature and evaporated. The solid was dissolved in dichloromethane, decolorized with the activated charcoal, filtered and evaporated to give an oily material which upon crystallization in methanol (-10˚C) afforded the title compound **237a** (2.38 g, 46% yield). MS (ESI)= 261 (MH^+).

Step 2: *N*-Hydroxy-6-[3-(4-oxo-4*H*-quinazolinyl)]hexanamide (**238a**)

[0459] Following the procedure described in Example 14, step 3, but substituting carboxylic acid 1*H*-benzo[d][1,3] oxazine-2,4-dione **237a** for 37, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound 238a was obtained in 23% yield. ^1H NMR: (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.66 (s, 1H), 8.38 (s, 1H), 8.14 (br d, J = 7.1 Hz, 1H), 7.81 (dd, J = 8.2,1.3 Hz, 1H), 7.66 (br d, J = 8.1 Hz, 1H), 7.53 (br t, J = 7.7 Hz, 1H), 3.95 (t, J = 7.1 Hz, 2H), 1.93 (t, J = 7.2 Hz, 2H), 1.72-1.62 (m, 2H), 1.56-1.46 (m, 2H), 1.30-1.23(m, 2H).

Example 142:

N-Hydroxy-6-[3-(4-oxo-4*H*-benzo[*d*][1,2,3]triazinyl)]hexanamide (238b)

Step 1: 6-[3-(4-Oxo-4*H*-benzo[*d*][1,2,3]triazinyl)]hexanoic acid (237b)

[0460] To a solution of 6-aminohexanoic acid (2.88 g, 20.00 mmol) in water (50 mL) was added triethylamine (3.06 ml, 22.00 mmol) followed by a portionwise addition of 1H-benzo[d][1,3]oxazine-2,4-dione (isatoic anhydride, 236) (3.26 g, 20.00 mmol). The reaction mixture was stirred for 2 hours at 30-40˚C, cooled to 0˚C, acidified with 20 mL 20% HCl

and treated with a solution of sodium nitrite (1.70 g, 25 mmol) in 10 mL water (over a 10 min period of time). The whole mixture was stirring at ambient temperature for 18 hours to form a solid which was collected by filtration, dried, dissolved in dichloromethane and decolorized with the activated charcoal, filtered and evaporated. The residual material was crystallized in a dichloromethane-hexane mixture at -10˚C to afford the title compound 237b in 75% yield. MS (ESI) = 262 (MH^+).

Step 2:*N*-Hydroxy-6-[3-(4-oxo-4*H*-benzo[*d*][1,2,3]triazinyl]hexanamide (238b)

[0461] Following the procedure described in Example 14, step 3, but substituting carboxylic acid 237b for 37, and using 1.1 equivalent of $NH_2OH.HCl$ and triethylamine each, the title compound 238b was obtained in 32%. ^1H NMR: (400 MHz, DMSO-D_6) δ 10.32 (s, 1H), 8.66 (s,1H), 8.25 (dd, J = 7.9,1.0 Hz,1H), 8.19 (br d, J = 7.7 Hz, 1H), 8.08 (dd, J = 7.2,1.4 Hz, 1H), 7.94 (dd, J = 7.2,1.4 Hz, 1H), 4.37 (t, J = 7.1 Hz, 2H),1.94 (t, J = 7.2 Hz, 2H), 1.85-1.75 (m, 2H), 1.58-1.48 (m, 2H), 1.35-1.27 (m, 2H).

Example 143:

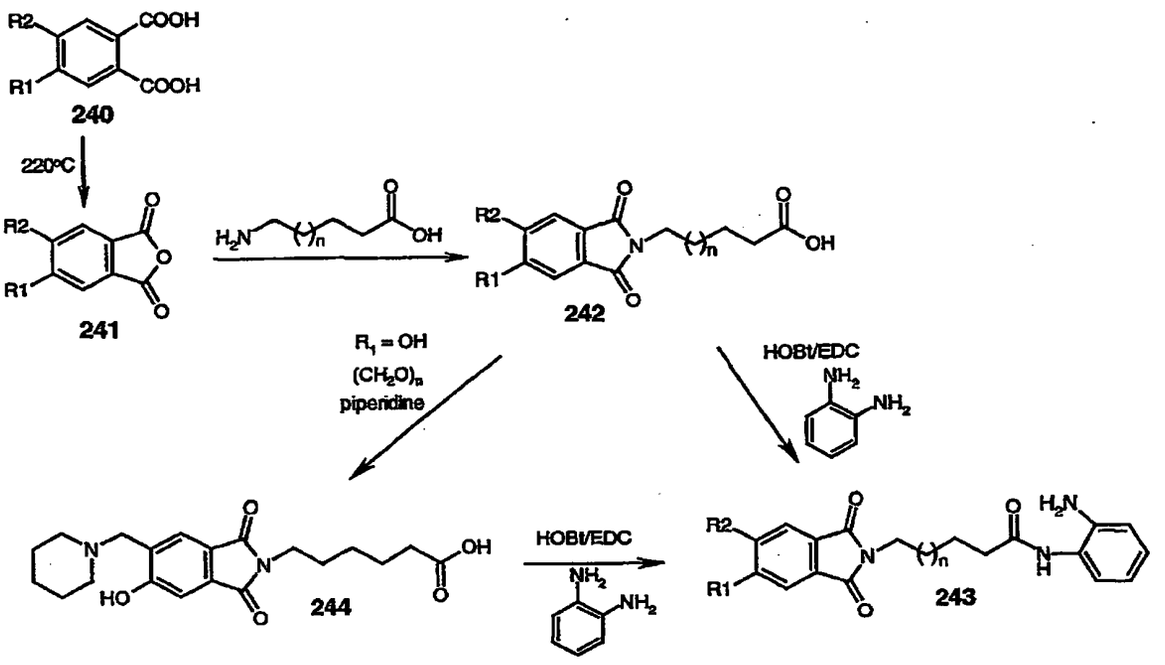
***N*-(2-Aminophenyl)-6-[3-(4-oxo-4*H*-quinazolinyl)]hexanamide (239a)**

[0462] Following the procedure described in Example 22, but substituting carboxylic acid **237a** for **50g**, the title compound **239a** was obtained in 25% yield. ^1H NMR: (400 MHz, DMSO-D_6) δ 9.08 (s, 1H), 8.41 (s, 1H), 8.17 (dd, J = 8.0, 1.1 Hz, 1H), 7.83 (dd, J = 8.4,1.5 Hz, 1H), 7.68 (br d, J = 8.1 Hz, 1H), 7.55 (dd, J = 8.0, 1.0 Hz, 1H), 7.12 (dd, J = 7.8, 1.1 Hz, 1H), 6.88 (dd, J = 8.0,1.3 Hz, 1H), 6.70 (dd, J = 7.9, 1.1 Hz, 1H), 6.51 (dd, J = 7.7,1.3 Hz, 1H), 4.80 (s, 2H), 3.99 (t, J = 7.3 Hz, 2H), 2.32 (t, J = 7.3 Hz, 2H), 1.77-1.70 (m, 2H), 1.67-1.60 (m, 2H), 1.39-1.33 (m, 2H).

Example 144:

***N*-(2-Aminophenyl)-6-[3-(4-oxo-4*H*-benzo[*d*][1,2,3]triazinyl]hexanamide (239b)**

[0463] Following the procedure described in Example 22, but substituting carboxylic acid **237b** for 50g, the title compound **239b** was obtained in 45% yield. ^1H NMR: (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.25 (dd, J = 7.9, 0.9 Hz, 1H), 8.19 (br d, J = 8.1 Hz, 1H), 8.08 (dd, J = 7.2,1.4 Hz, 1H), 7.92 (dd, J = 8.2,1.2 Hz, 1H), 7.09 (dd, J = 7.8,1.2 Hz, 1H), 6.87 (dd, J = 8.5,1.4 Hz, 1H), 6.69 (dd, J = 8.0,1.3 Hz, 1H), 6.49 (dd, J = 7.8,1.4 Hz, 1H), 4.78 (s, 2H), 4.39 (t, J = 7.1 Hz, 2H), 2.28 (t, J = 7.4 Hz, 2H), 1.90-1.82 (m, 2H), 1.69-1.58 (m, 2H), 1.43-1.34 (m, 2H).



243a : n = 2, R_1 = R_2 = H (Example 145)

243b : n = 1, R_1 = R_2 = H (Example 146)

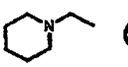
243c : n = 3, R_1 = R_2 = H (Example 147)

243d : n = 2, R_1 = CH_3, R_2 = H (Example 148)

243e : n = 2, R_1 = NO_2, R_2 = H (Example 149)

243f : n = 2, R_1 = R_2 = Cl (Example 150)

243g : n = 2, R_1 = OH, R_2 = H (Example 151)

243h : n = 2, R_1 = OH, R_2 =  **(Example 152)**

[0464] Examples 145 to 152 are for illustration purpose only.

Example 145:

***N*-(2-Aminophenyl)-6-(*N*-phthaloyl)hexanamide (243a)**

Step 1: 6-*N*-Phthaloylhexanoic acid (**242a**)

[0465] To a solution of phthalic anhydride 241a (1.48 g, 10.00 mmol) in anhydrous ethyl alcohol (20 mL) was added 6-aminocaproic acid (1.97 g, 15.00 mmol). The reaction mixture was refluxed for 16 hours, cooled to room temperature, evaporated to dryness to produce a solid material, which was triturated with water to form a suspension. The suspension was filtered, the solid was collected and dried to afford the title compound **242a** (1.18 g, 45% yield). ^{1}H NMR: (400 MHz, DMSO-d6) δ 7.87-7.80 (m, 4H), 3.54 (t, J = 7.1 Hz, 2H), 2.17 (t, J = 7.3 Hz, 2H), 1.62-1.44 (m, 4H), 1.30-1.23 (m, 2H).

Step 2: *N*-(2-Aminophenyl)-6-(*N*-phthaloyl)hexanamide (**243a**)

[0466] Following the procedure described in Example 22, but substituting carboxylic acid **242a** for **50g**, the title compound **243a** was obtained in 31% yield. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 7.88-7.80 (m, 4H), 7.09 (dd, J =

7.8, 1.4 Hz, 1H), 6.86 (dd, J = 8.0, 1.5 Hz, 1H), 6.68 (dd, J = 8.0,1.4 Hz, 1H), 6.49 (dd, J = 7.8,1.5 Hz, 1H), 4.80 (s, 2H), 3.57 (t, J = 7.0 Hz, 2H), 2.28 (t, J = 7.3 Hz, 2H), 1.64-1.57 (m,4H), 1.37-1.27 (m, 2H),

Example 146:

***N*-(2-Aminophenyl)-5-(N-phthaloyl)pentanamide (243b)**

Step 1: 5-(*N*-Phthaloyl)pentanoic acid (**242b**)

[0467] Following a procedure analogous to that described in Example 145, step 1, but substituting 5-amino-valeric acid for 6-amino-caproic acid, the title compound **242b** was obtained in 46% yield. MS (ESI) = 270 ($M+Na^+$).

Step 2: *N*-(2-Aminophenyl)-5-(*N*-phthaloy)-pentanamide (**243b**)

[0468] Following the procedure described in Example 22, but substituting carboxylic acid **242b** for **50g**, the title compound **243b** was obtained in 28% yield. ^1H NMR: (300 MHz, DMSO-d6) δ 9.06 (s, 1H), 7.87-7.80 (m, 4H), 7.11 (d, J = 7.7 Hz, 1H), 6.86 (t, J = 7.4 Hz, 1H), 6.68 (dd, J = 8.0,1.4 Hz, 1H), 6.50 (dd, J = 8.8, 1.1 Hz, 1H), 4.78 (br s, 2H), 3.59 (t, J = 5.8 Hz, 2H), 2.33 (t, J = 6.6 Hz, 2H), 1.60 (m, 4H).

Example 147:

***N*-(2-Aminophenyl)-7-(*N*-phthaloyl)heptanamide (243c)**

Step 1: 7-(*N*-Phthaloyl)heptanoic acid (**242c**)

[0469] Following a procedure analogous to that described in Example 145, step 1, but substituting 7-aminoheptanoic acid for 6-amino-caproic acid, the title compound **242c** was obtained in 46% yield. MS (ESI) = 298 (MH^+).

Step 2: *N*-(2-Aminophenyl)-7-(*N*-phthaloyl)-heptanamide (**243c**)

[0470] Following the procedure described in Example 22, but substituting carboxylic acid **242c** for **50g**, the title compound **243c** was obtained in 28% yield. ^1H NMR: (300 MHz, DMSO-d_6 δ 9.05 (s, 1H), 7.87-7.79 (m, 4H), 7.11 (d, J = 7.7 Hz, 1H), 6.86 (t, J = 7.4 Hz,1H), 6.68 (d, J = 8.0 Hz, 1H), 6.50 (t, J = 7.7 Hz, 1H), 4.77 (s, 2H), 3.55 (t, J = 7.1 Hz, 2H), 2.27 (t, J = 7.4 Hz, 2H), 1.61-1.53 (m, 4H), 1.31-1.28 (m, 4H).

Example 148:

***N*-(2-Aminophenyl)-6-(5-methyl-*N*-phthaloyl)hexanamide (243d)**

Step 1: 6-(5-Methyl-*N*-phthaloyl)hexanoic acid (**242d**)

[0471] Following a procedure analogous to that described in Example 145, step 1, but substituting 5-methyl-*N*-phthaloyl for *N*-phthaloyl, the title compound **242d** was obtained in 85% yield. MS (ESI) = 276 (MH^+).

Step 2: *N*-(2-Aminophenyl)-6-(5-methyl-*N*-phthaloy)hexanamide (**243d**)

[0472] Following the procedure described in Example 22, but substituting carboxylic acid **242d** for **50g**, the title compound **243d** was obtained in 43% yield. ^1H NMR: (300 MHz, DMSO-d_6) δ 9.04 (s, 1H), 7.73-7.60 (m, 3H), 7.07 (d, J = 7.7 Hz, 1H), 6.85 (t, J = 8.0 Hz, 1H), 6.67 (dd, J = 8.0,1.1 Hz, 1H), 6.50 (t, J = 7.7 Hz, 1H), 4.77 (s, 2H), 3.52 (t, J = 7.1 Hz, 2H), 2.46 (s, 3H, CH3), 2.27 (t, J = 7.1 Hz, 2H), 1.58 (br s, 4H), 1.32-1.22 (m, 2H).

Example 149:

***N*-(2-Aminophenyl)-6-(5-nitro-*N*-phthaloyl)hexanamide (243e)**

Step 1: 6-(5-Nitro-*N*-phthaloyl)hexanoic acid (**242e**)

[0473] Following a procedure analogous to that described in Example 145, step 1, but substituting 5-nitro-*N*-phthaloyl

for *N*-phthaloyl, the title compound **242e** was obtained in 26% yield. MS (ESI) = 305 (MH^+).

Step 2: *N*-(2-Aminophenyl)-6-(5-nitro-*N*-phthaloyl)hexanamide (**243e**)

[0474] Following the procedure described in Example 22, but substituting carboxylic acid **242e** for **50g**, the title compound **243e** was obtained in 14% yield. ^1H NMR: (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.60 (dd, J = 8.2 Hz, 1.9 Hz, 1H), 8.47 (d, J =1.5 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.10 (dd, J = 7.9,1.3 Hz, 1H), 6.86 (dd, J = 8.0, 1.5 Hz, 1H), 6.67 (dd, J = 1.3, J = 8.0 Hz, 1H), 6.49 (dd, J = 7.7,1.4 Hz, 1H), 4.76 (s, 2H,), 3.62 (t, J = 7.0 Hz, 2H), 2.29 (t, J = 7.3 Hz, 2H), 1.71-1.55 (m, 4H), 1.38-1.30 (m, 2H).

Example 150:

***N*-(2-Aminophenyl)-6-(5,6-dichloro-*N*-phthaloyl)hexanamide (243f)**

Step 1: 6-(5,6-Dichloro-*N*-phthaloyl)hexanoic acid (**242f**)

[0475] Following a procedure analogous to that described in Example 145, step 1, but substituting 5,6-dichloro-*N*-phthaloyl for *N*-phthaloyl, the title compound **242f** was obtained in 64% yield. MS (ESI) = 328 (MH^+).

Step 2: *N*-(2-Aminophenyl)-6-(5,6-dichloro-*N*-phthaloyl)hexanamide (**243**)

[0476] Following the procedure described in Example 22, but substituting carboxylic acid **242f** for 50g, the title compound **243f** was obtained in 52% yield. ^1H NMR: (300 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.15 (s, 2H), 7.07 (d, J = 7.4 Hz, 1H), 6.85 (t, J = 7.8 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.48 (t, J = 7.7 Hz, 1H), 4.76 (s, 2H), 3.56 (t, J = 6.9 Hz, 2H), 2.27 (t, J = 7.1 Hz, 2H), 1.63-1.56 (m, 4H), 1.34-1.27 (m, 2H).

Example 151:

***N*-(2-Aminophenyl)-6-(5-hydroxy-*N*-phthaloyl)hexanamide (243g)**

Step 1: 6-(5-Hydroxy-*N*-phthaloyl)hexanoic acid (**242g**)

[0477] 4-Hydroxy-phthalic acid **240** (2.30 g, 12.64 mmol) was heated for two hours at 220˚C under vacuum, cooled to room temperature and dissolved in 50 mL anhydrous ethyl alcohol. To this solution 6-amino caproic acid (2.48 g, 18.93 mmol) was added and the mixture was refluxed for 28 hours, cooled and evaporated to produce an oily residue. This material was triturated with water to form a precipitate which was collected and dried to afford the title compound **242g** (2.24 g, 64% yield). MS (ESI) = 276 (MH^+).

Step 2: *N*-(2-Aminophenyl)-6-(5-hydroxy-*N*-phthaloyl)hexanamide (**243g**)

[0478] Following the procedure described in Example 22, but substituting carboxylic acid **242g** for **50g**, the title compound **243g** was obtained in 11% yield. ^1H NMR: (300 MHz, DMSO-d6) δ 10.88 (br s, 1H), 9.04 (s, 1H), 7.71 (d, J = 8.0 Hz, 4H), 7.11-7.07 (m, 3H), 6.86 (d, J = 6.3 Hz, 1H), 6.68 (d, J = 6.3 Hz, 1H), 6.49 (t, J = 7.4 Hz, 1H), 4.77 (s, 2H), 3.51 (t, J = 7.1 Hz, 2H), 2.27 (t, J = 7.4 Hz, 2H), 1.62-1.54 (m, 4H), 1.37-1.25 (m, 2H).

Example 152:

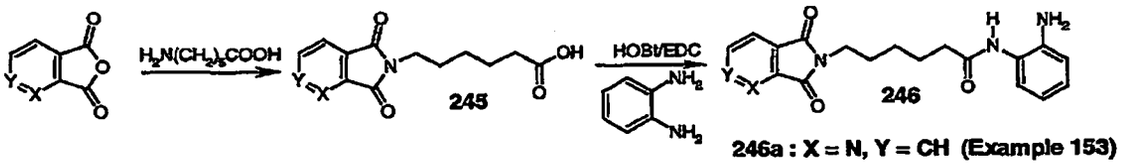
***N*-(2-Amminophenyl)-6-(5-hydroxy-6-(1-methylpiperidinyl)-*N*-phthaloyl)-hexanamide (243h)**

Step 1: 6-(5-Hydroxy-6-(1-methylpiperidinyl)-*N*-phthaloyl)hexanoic acid (**244**)

[0479] To a stirring suspension of the phthalimido acid **242g** (500 mg, 1.81 mmol) in a mixture of anhydrous dioxane (7 mL) and anhydrous DMF (3.5 mL) at room temperature was added paraformaldehyde (73 mg, 2.4 mmol) followed by addition of piperidine (0.22 mL, 2.2 mmol). The reaction mixture was stirred at 80˚C for 8 hours, solvents were removed in vacuum and the crude residue was purified by column chromatography using a gradient of 100% dichloromethane to 5% methanol in dichloromethane. The resulting yellow solid was crystallized from methanol-diethyl ether to afford the title compound 244 (0.25 g, 37%). MS (ESI) = 375 (MH^+).

Step 2: *N*-(2-Aminophenyl)-6-(5-hydroxy-6-(1-methylpiperidinyl)-*N*-phthaloyl) hexanamide (**243h**)

[0480] Following the procedure described in Example 22, but substituting carboxylic acid **244** for 50g, the title compound **243h** was obtained in 44% yield. 1HNMR: (300 MHz, DMSO-d6) δ 9.04 (s, 1H), 7.58 (s, 1H), 7.07 (d, J = 7.97 Hz, 1H), 7.02 (s, 1H), 6.85 (t, J = 7.69 Hz, 1H), 6.67 (d, J = 7.97 Hz, 1H), 6.48 (t, J = 7.69 Hz, 1H), 4.76 (br s, 2H), 3.75 (s, 2H), 3.50 (t, J = 6.87 Hz, 2H), 2.26 (t, J = 7.28 Hz, 2H), 1.54 (m, 8H), 1.44 (m, 2H), 1.27 (m, 2H).



[0481] Examples 153-154 are for illustration purpose only.

Example 153:

***N*-(2-Aminophenyl)-6-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-*b*]pyridinyl)] hexanamide (246a)**

Step 1: 5-[6-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-*b*]pyridinyl)]hexanoic acid (**245a**)

[0482] Following a procedure analogous to that described in Example 145, step 1, but substituting 2,3-pyridinedicarboxylic anhydride, for N-phthalic anhydride, the title compound 245a was obtained in 22% yield. MS (ESI) = 363 (MH^+).

Step 2: *N*-(2-Aminophenyl)-[6-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-*b*]pyridinyl]-hexamamide (**246a**)

[0483] Following the procedure described in Example 22, but substituting carboxylic acid **245a** for **50g**, the title compound **246a** was obtained in 40% yield. ^{1}H NMR: (300 MHz, DMSO-d6) δ 9.06 (s, 1H), 8.94 (dd, J = 4.9,1.4 Hz,1H), 8.27 (dd, J = 7.7,1.4 Hz, 1H), 7.75 (dd, J = 7.7, 4.9 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.85 (t, J = 8.2 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.49 (t, J = 7.7 Hz, 1H), 4.76 (s, 2H), 3.60 (t, J = 7.1 Hz, 2H), 2.28 (t, J = 6.9 Hz, 2H), 1.63-1.57 (m, 4H), 1.35-.28 (m, 2H).

Example 154:

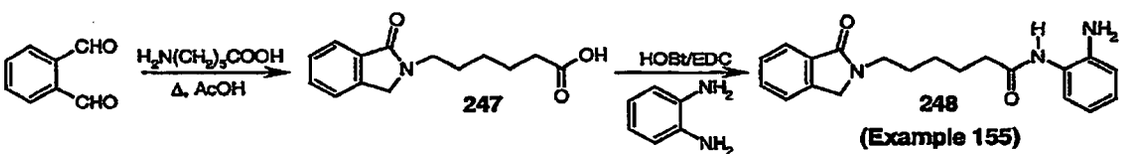
***N*-(2-Aminophenyl)-6-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-*c*]pyridinyl)] hexanamide (246b)**

Step 1: 5-[6-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-*c*]pyridinyl)]hexanoic acid (**245b**)

[0484] Following a procedure analogous to that described in Example 145, step 1, but substituting 3,4-pyridinedicarboxylic anhydride for N-phthalic anhydride, the title compound 245b was obtained in 8% yield. MS (ESI) = 363 (MH^+).

Step 2: *N*-(2-Aminophenyl)-6-[6-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-*c*]pyridinyl] hexanamide (**246b**)

[0485] Following the procedure described in Example 22, but substituting carboxylic acid 245b for 50g, the title compound 246b was obtained in 61% yield. ^{1}H NMR: (300 MHz, DMSO-d6) 8 9.05-9.09 (m, 3H), 7.87 (d, J = 4.7Hz, 1H), 7.08 (d, J = 7.4 Hz, 1H), 6.86 (t, J = 7.1 Hz, 1H), 6.67 (d, J = 6.9 Hz, 1H), 6.49 (t, J = 6.3 Hz, 1H), 4.77 (s, 2H), 3.58 (t, J = 6.9 Hz, 2H), 2.28 (t, J = 7.1 Hz, 2H), 2.00-1.90 (m, 2H), 1.64-1.54 (m, 4H), 1.33-1.29 (m, 2H).



[0486] Example 155 are for illustration purpose only.

Example 155:

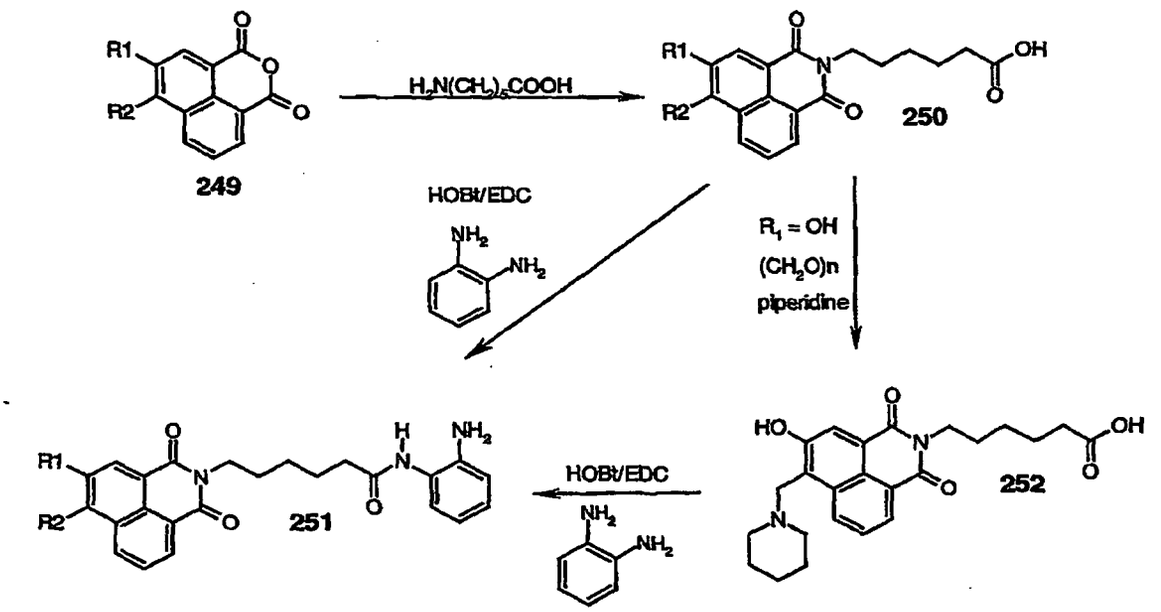
***N*-(2-Aminophenyl)-6-[2-(1-oxo-1,3-dihydro-isoindolyl)]hexanamide (248)**

Step 1: 6-[2-(1-Oxo-1,3-dihydro-isoindolyl)]hexanoic acid (**247**)

[0487] To a solution of benzene-1,2-carbaldehyde (670 mg, 5.00 mmol) in acetic acid (6 mL) was added 6-amino-hexanoic acid (655 mg, 5.00 mmol). The reaction mixture was refluxed for 15 minutes, cooled to room temperature and evaporated. The residue was chromatographed on a silica gel column (5% to 10% methanol in dichloromethane) to produce the title compound 247 (1.20 g, 97% yield), MS (ESI) = 248 (MH^+).

Step 2: *N*-(2-Aminophenyl)-6-[2-(1-oxo-1,3-dihydro-isoindolyl)]hexanamide (**248**)

[0488] Following the procedure described in Example 22, but substituting carboxylic acid **247** for **50g**, the title compound 248 was obtained in 27% yield. ^{1}H NMR: (300 MHz, DMSO-d6) δ 9.06 (s, 1H), 7.66-7.46 (m, 4H), 7.09 (d, J = 8.0 Hz, 1H), 6.86 (t, J = 7.7 Hz, 1H), 6.68 (d, J = 7.7 Hz, 1H), 6.49 (t, J = 7.7 Hz, 1H), 4.78 (s, 2H), 4.45 (s, 2H), 3.51 (t, J = 6.9 Hz, 2H), 2.29 (t, J = 7.1 Hz, 2H), 1.63-1.60 (m, 4H), 1.33-1.27 (m, 2H).



251a : R1 = OH, R2 = H (Example 156)

251b : R1 = H, R2 = Br (Example 157)

251c : R1 = OH, R2 =  **(Example 158)**

[0489] Examples 156-158 are for illustration purpose only.

Example 156:

***N*-(2-Aminophenyl)-6-[2-(5-hydroxy-1,3-dioxo-1*H*,3*H*-benzo[de]isoquinolinyl)]-hexanamide (251a)**

Step 1: 6-[2-(5-Hydroxy-1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolinyl)]hexanoic acid (**250a**)

[0490] Following a procedure analogous to that described in Example 145, step 1, but substituting 3-hydroxy-1,8-naphthalic anhydride for N-phthalic anhydride, the title compound 250a was obtained in 98% yield. MS (ESI) = 328 (MH^+).

Step 2: *N*-(2-Aminophenyl)-6-[2-(5-hydroxy-1,3-dioxo-1*H*,3*H*-benzo[de]isoquinolinyl)]-hexanamide (**251a**)

[0491] Following the procedure described in Example 22, but substituting carboxylic acid **250a** for **50g**, the title compound **251a** was obtained in 18% yield. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 9.07 (s, 1H), 8.22 (t, J = 6.5 Hz, 2H), 8.00 (d, J = 2.4 Hz, 1H), 7.72 (t, J = 7.4 Hz, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.09 (dd, J = 7.8 Hz, 1.3 Hz, 1H), 6.87 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.69 (dd, J = 8.0 Hz, 1.3 Hz, 1H), 6.49 (dd, J = 7.7 Hz, 1.4 Hz, 1H), 4.81 (s, 2H), 4.02 (t, J = 7.3 Hz, 2H), 2.31 (t, J = 7.3 Hz, 2H), 1.67-1.58 (m, 4H), 1.42-1.35 (m, 2H).

Example 157:

***N*-(2-Aminophenyl)-6-[2-(6-bromo-1,3-dioxo-1*H*,3*H*-benzo[de]isoquinolinyl)]-hexanamide (251b)**

Step 1: 6-[2-(6-Bromo-1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolinyl)]hexanoic acid (**250b**)

[0492] Following a procedure analogous to that described in Example 145, step 1, but substituting 4-bromo-1,8-naphthalic anhydride for *N*-phthalic anhydride, the title compound **250a** was obtained in 96% yield. MS (ESI) = 390 (MH^+).

Step 2: *N*-(2-Aminophenyl)-6-[2-(6-bromo-1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolinyl)]-hexanamide (**251b**)

[0493] Following the procedure described in Example 22, but substituting carboxylic acid **250b** for 50g, the title compound **251b** was obtained in 26% yield. ^{1}H NMR: (300 MHz, DMSO-d6) δ 9.05 (s, 1H, NH), 8.52 (t, J = 8.2 Hz, 2H), 8.30 (d, J = 7.7 Hz, 1H), 8.18 (d, J = 7.7 Hz, H), 7.96 (t, J = 7.7 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.85 (t, J = 8.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.47 (t, J = 7.7 Hz, 1H), 4.78 (br s, 2H), 4.02 (t, J = 7.1 Hz, 2H), 2.30 (t, J = 7.1 Hz, 2H), 1.66-1.58 (m, 4H), 1.41-1.34 (m, 2H).

Example 158:

***N*-(2-Aminophenyl)-6-[2-(5-hydroxy-1,3-dioxo-6-(1-methylpiperidynyl)-1*H*,3*H*-benzo[*de*]isoquinolinyl)]-hexanamide (251c)**

Step 1: 6-[2-(5-Hydroxy-1,3-dioxo-6-piperidyn-1-ylmethyl-1*H*,3*H*-benzo[*de*]isoquinolin)]hexanoic acid (**252**)

[0494] To a stirring suspension of the acid **250a** (390 mg, 1.19 mmol) in a mixture of anhydrous dioxane (5 mL) and anhydrous DMF (2 mL) at room temperature was added paraformaldehyde (70 mg, 2.33 mmol) followed by addition of piperidine (0.14 mL, 1.42 mmol). The reaction mixture was stirred for 18 hours at ambient temperature, solvents were removed in vacuum and the crude residue was triturated with 0.5 mL methanol followed by addition of 25 mL ether. The formed suspension was filtered to afford the title compound **252** as yellow crystals (424 mg, 84%). MS (ESI) = 425 (MH^+).

Step 2: *N*-(2-Aminophenyl)-6-[2-(5-hydroxy-1,3-dioxo-6-(1-methylpiperidynyl)-1*H*,3*H*-benzo[*de*]isoquinolinyl)]hexanamide (**251c**)

[0495] Following the procedure described in Example 22, but substituting carboxylic acid **252** for **50g**, the title compound **251c** was obtained in 39% yield. ^{1}H NMR: (300 MHz, DMSO-d6) δ 9.05 (s, 1H), 8.43 (d, J = 8.2 Hz, 1H), 8.27 (d, J = 7.1 Hz, 1H), 7.96 (s, 1H), 7.75 (t, J = 8.2 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.85 (t, J = 6.7 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.47 (t, J = 7.1 Hz, 1H), 4.77 (s, 2H), 4.15 (s, 2H), 4.02 (t, J = 6.9 Hz, 2H), 2.54 (br s, 4H), 2.30 (t, J = 7.1 Hz, 2H), 1.65-1.36 (m, 12H).

Example 159:

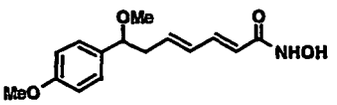
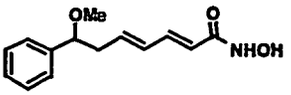
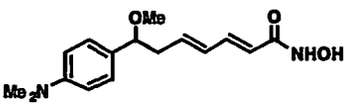
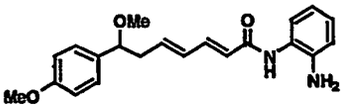
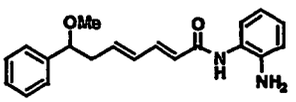
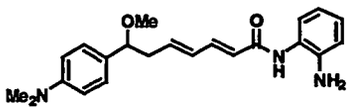
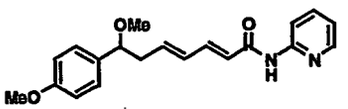
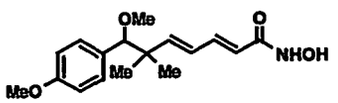
Inhibition of Histone Deacetylase Enzymatic Activity

[0496] HDAC inhibitors were screened against histone deacetylase enzyme in nuclear extracts prepared from the human small cell lung cancer cell line H446 (ATTC HTB-171) and against a cloned recombinant human HDAC-1 enzyme expressed and purified from a Baculovirus insect cell expression system.

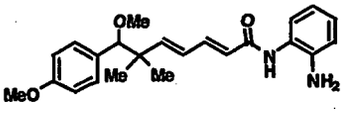
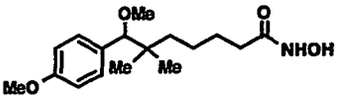
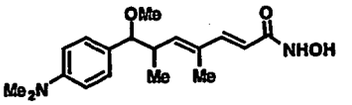
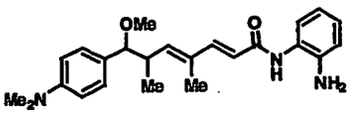
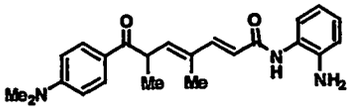
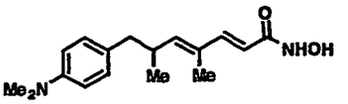
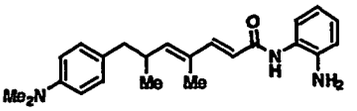
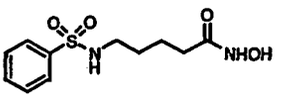
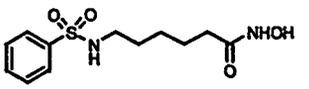
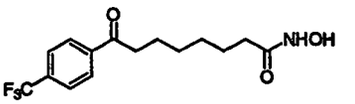
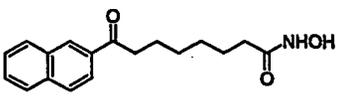
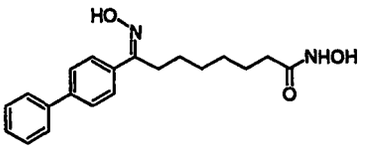
[0497] For deacetylase assays, 20,000 cpm of the [^{3}H]-metabolically labeled acetylated histone substrate (M. Yoshida et al., J. Biol. Chem. 265(28): 17174-17179 (1990)) was incubated with 30 μg of H446 nuclear extract or an equivalent amount of the cloned recombinant hHDAC-1 for 10 minutes at 37˚C. The reaction was stopped by adding acetic acid (0.04 M, final concentration) and HCl (250 mM, final concentration). The mixture was extracted with ethyl acetate and the released [^{3}H]-acetic acid was quantified by scintillation counting. For inhibition studies, the enzyme was preincubated with compounds at 4 ˚C for 30 minutes prior to initiation of the enzymatic assay. IC_{50} values for HDAC enzyme inhibitors were determined by performing dose response curves with individual compounds and determining the concentration of inhibitor producing fifty percent of the maximal inhibition.

[0498] Representative data are presented in Table 2. In the first column are reported IC_{50} values determined against histone deacetylase in nuclear extracts from H446 cells (pooled HDACs). In the second column are reported IC_{50} values determined against recombinant human HDAC-1 enzyme (rHDAC-1).

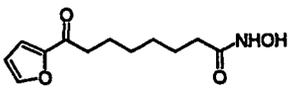
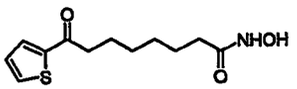
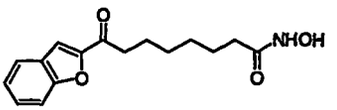
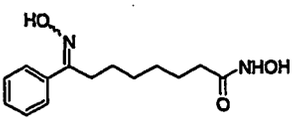
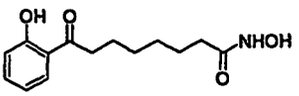
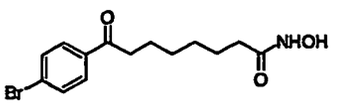
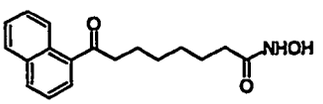
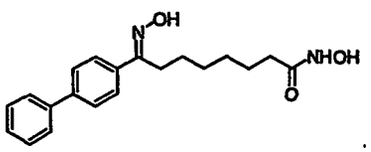
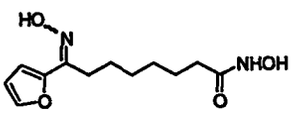
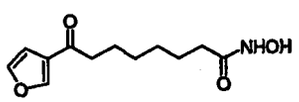
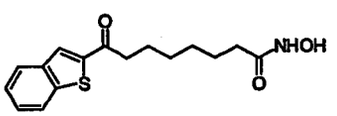
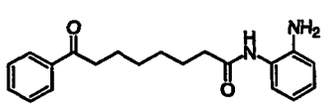
Table 2: Inhibition of Histone Deacetylase

Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex.1	6		3	0.25
Ex. 2	12		9.4	ND
Ex. 3	17		4	0.25
Ex. 4	18		> 100	1
Ex. 5	19		> 100	<20
Ex. 6	20		> 20	3
Ex. 7	21		> 100	ND
Ex. 8	26		5	1

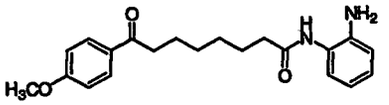
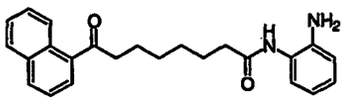
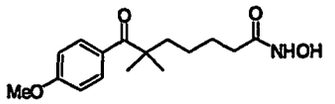
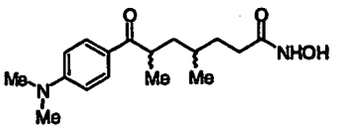
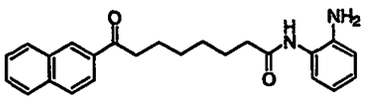
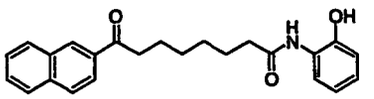
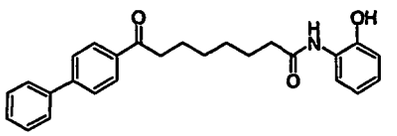
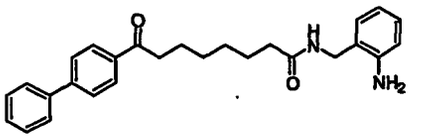
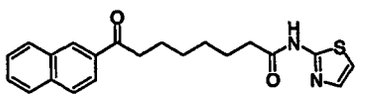
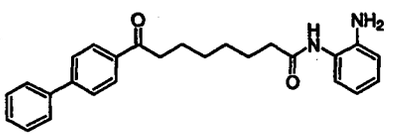
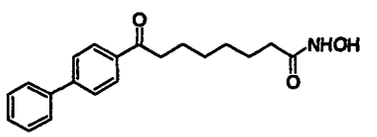
(continued)

Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 9	27		> 100	ND
Ex. 10	28		4	0.1
Ex. 11	33		>10	ND
Ex. 12	34		> 100	7
Ex. 13	35		> 100	2
Ex. 14	38		> 20	ND
Ex. 15	39		> 20	7
Ex. 16	42		6	1
Ex. 17	47		4.5	0.5
Ex. 18	52c		0.55	0.06
Ex. 18	52g		0.03	0.005
Ex. 18	(Z)-51h		75%	

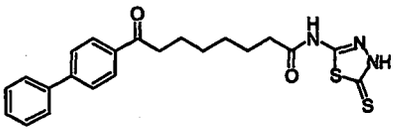
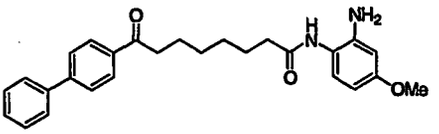
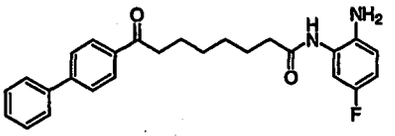
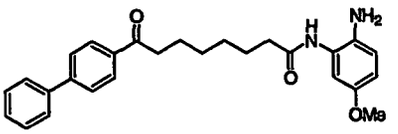
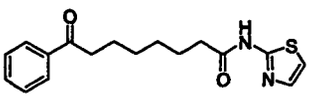
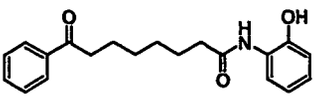
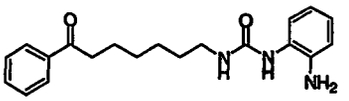
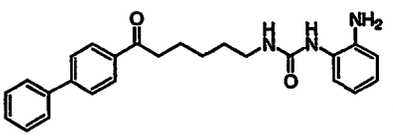
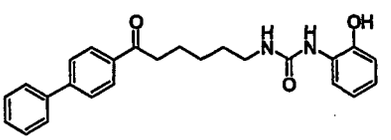
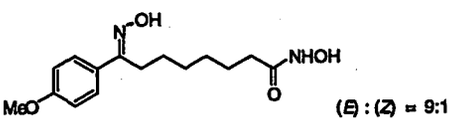
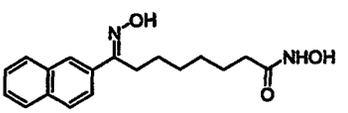
(continued)

Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 18	52i		3	0.1
Ex. 18	52k		0.9	0.18
Ex. 18	52l		0.3	0.03
Ex. 18	51a		0.35	0.1
Ex. 18	52e		0.55	0.06
Ex. 18	52d		0.05	0.055
Ex. 18	52f		0.55	0.01
Ex. 18	(E)-51h		99%	
Ex. 18	51i		0.9	0.1
Ex. 18	52j		3	0.45
Ex. 18	52m		0.1	0.01
Ex. 19	53a			0.6

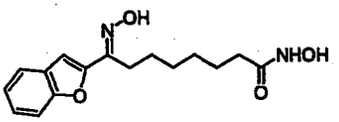
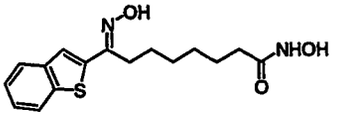
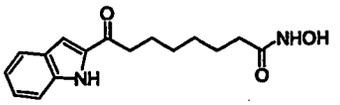
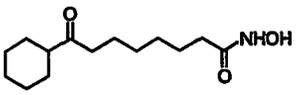
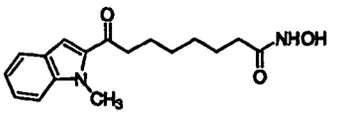
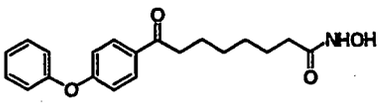
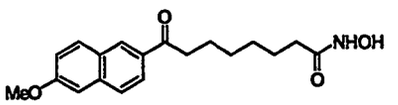
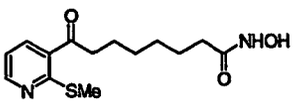
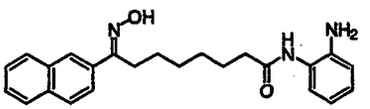
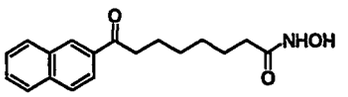
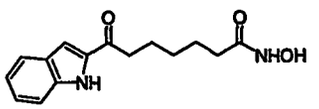
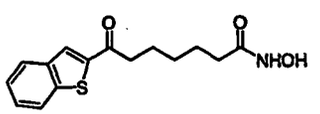
(continued)

Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 19	53b		0%	1
Ex. 19	53f		3%	2
Ex. 20	58		3	0.25
Ex. 21	62		1.1	
Ex. 22	63		> to	2.2
Ex. 25	66		0%	2.3
Ex. 29	74		0%	7.8
Ex. 30	75		0%	8.4
Ex. 31	76			23
Ex. 32	77		11%	1.9
Ex. 33	78		0.04	0.004

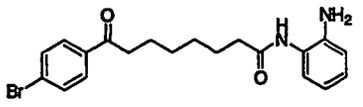
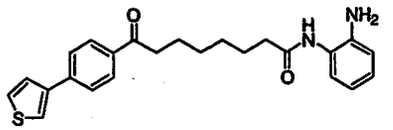
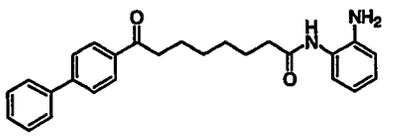
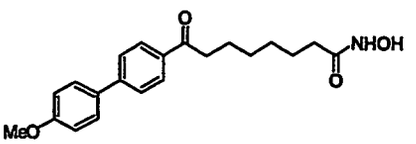
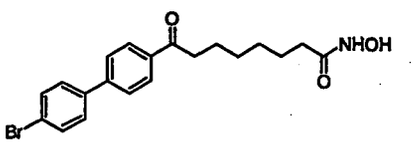
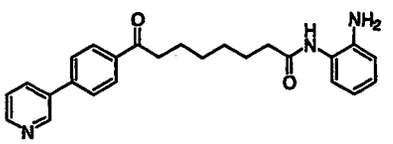
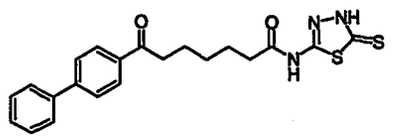
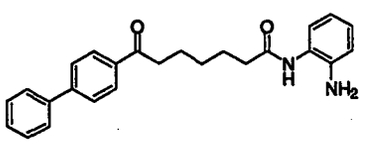
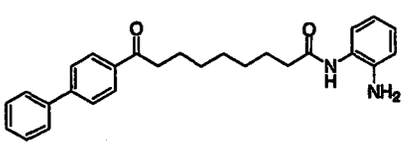
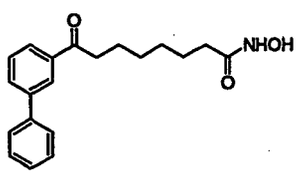
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Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 34	79			9
Ex. 36	81		27%	25
Ex. 37	82			20
Ex. 38	83			25
Ex. 40	85			20
Ex. 41	86			5
Ex. 43	89		0%	16.3
Ex. 44	92		0%	15.9
Ex. 45	93		0%	6.4
Ex. 48	96	 (E) : (Z) = 9:1	0.1	0.035
Ex. 49	97		0.03	0.01

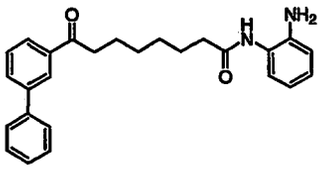
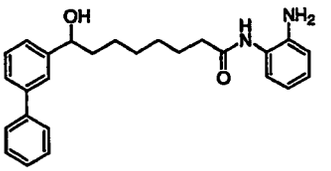
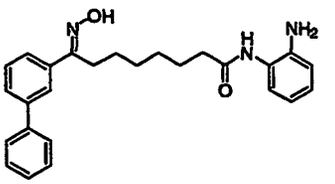
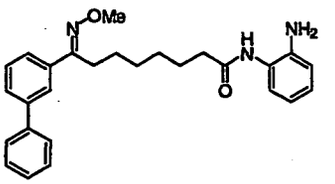
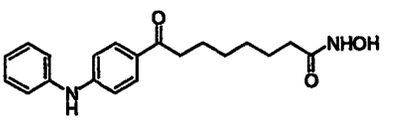
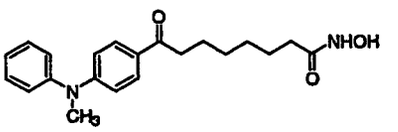
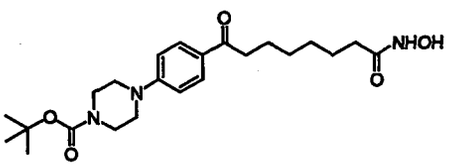
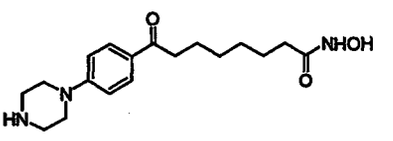
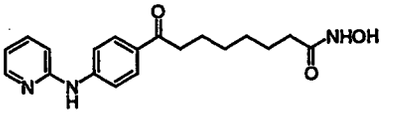
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Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 50	98		0.04	0.03
Ex. 51	99		0.035	0.008
Ex. 52	100			4
Ex. 54	102			
Ex. 55	103		0.1	0.05
Ex. 56	104		61% @1μM	0.16
Ex. 57a	105a		83% @1μM	0.01
Ex. 57b	105b		40% @1μM	0.02
Ex. 58	106		> 20	4
Ex. 63	111		0.35	0.2
Ex. 64	112		0.5	0.039
Ex. 65	113		33% @1μM	0.13

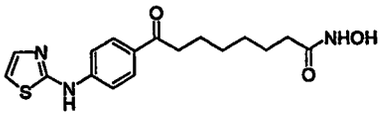
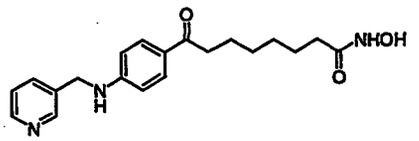
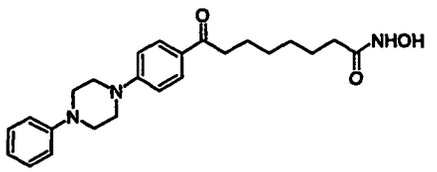
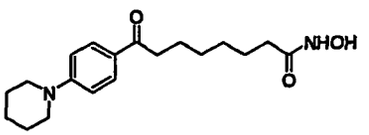
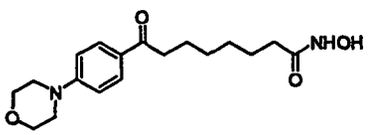
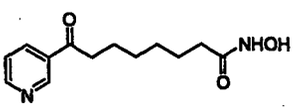
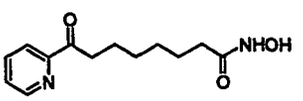
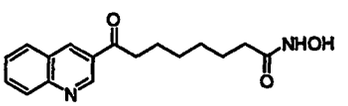
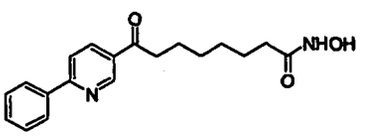
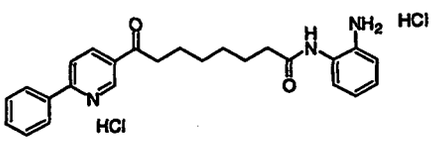
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Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 66	114		> 20	6.3
Ex. 67	117		0%	9
Ex. 68	123			4
Ex. 69	120		83%	0.002
Ex. 70	124			0.001
Ex. 71	127		0%	10.3
Ex. 72	128			19
Ex. 73	129			1
Ex. 74	130			3
Ex. 75	131			0.008

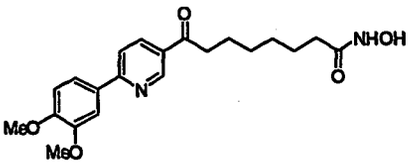
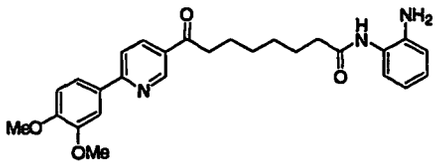
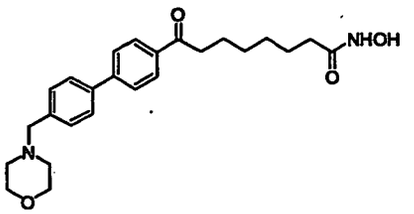
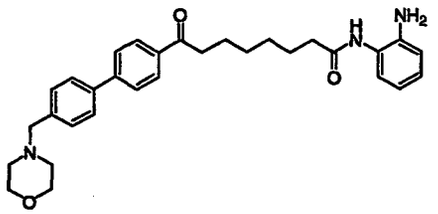
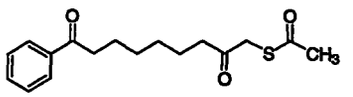
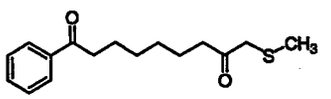
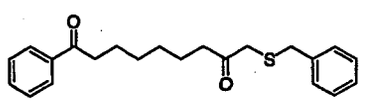
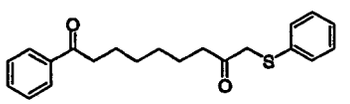
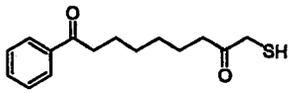
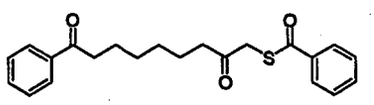
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Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 76	132			0.8
Ex. 77	133			1
Ex. 78	134			1
Ex. 79	135			2
Ex. 80	138a		83% @ 1μM	0.004
Ex. 81	138b		0.049	0.008
Ex. 82a	138c1			0.03
Ex. 82b	138c2			0.03
Ex. 83	138d		0.02	0.004

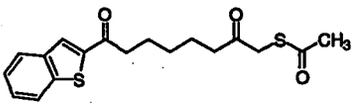
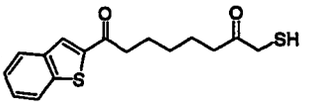
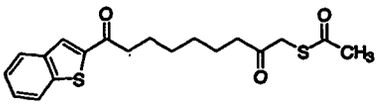
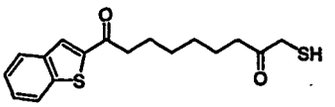
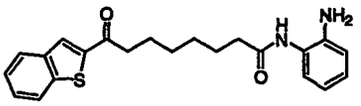
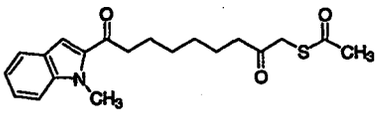
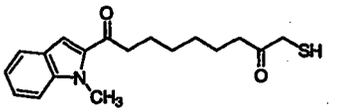
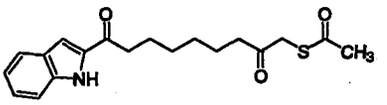
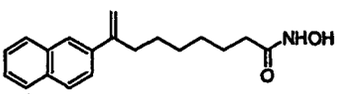
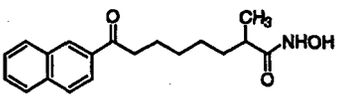
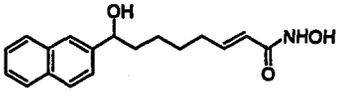
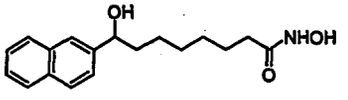
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Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 84	138e		0.02	0.004
Ex. 85	138f			0.02
Ex. 86	138g		0.051	0.006
Ex. 87	138h		0.048	0.009
Ex. 88	138i		0.1	0.033
Ex. 89a	141a1		22% ®1μM	0.06
Ex. 89b	141a2		12% @1μM	
Ex. 90	141b		71% @1μM	0.035
Ex. 91	145			0.008
Ex. 92	146			2

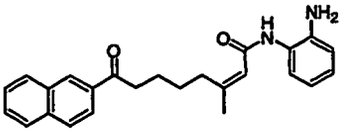
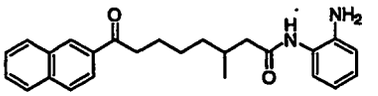
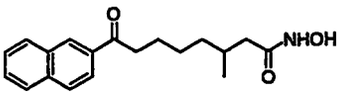
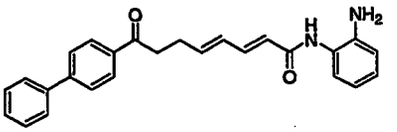
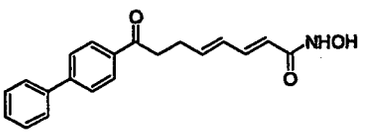
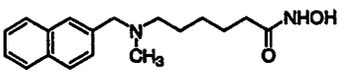
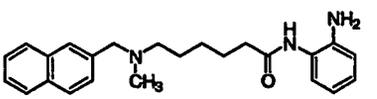
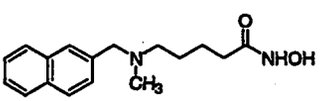
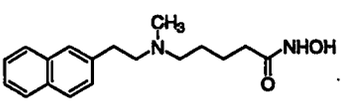
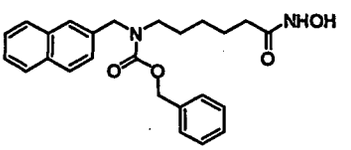
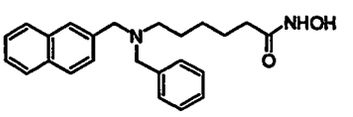
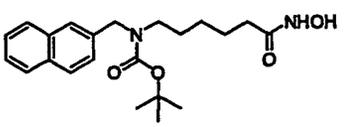
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Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 93	150			0.05
Ex. 94	151			4
Ex. 95	156			20
Ex. 96	157			4
Ex. 97	159a		0.05	0.1
Ex. 98	159b		14% @5μM	0.5
Ex. 99	159c		0% @5μM	5
Ex. 100	159d		50	5
Ex. 101	159e		0.05	0.05
Ex. 102	159f		0.35	0.7

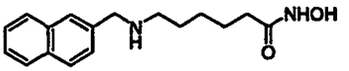
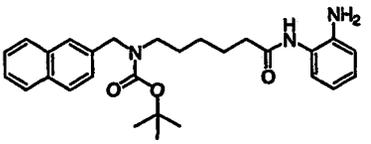
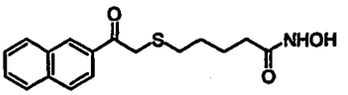
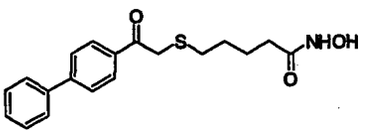
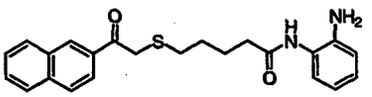
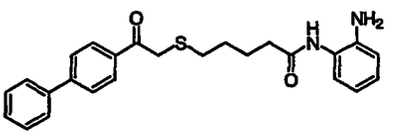
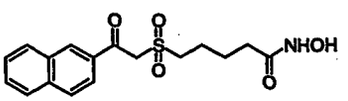
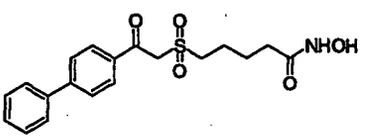
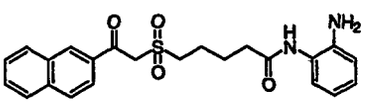
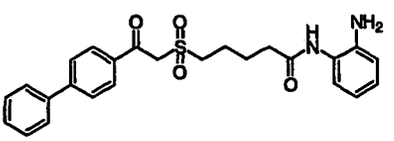
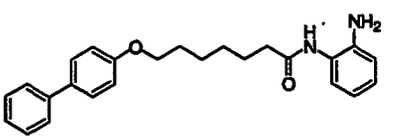
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Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 103	160		0.08	0.13
Ex. 104	161		0.094	0.071
Ex. 105	162		0.04	0.035
Ex. 106	163		0.04	0.04
Ex. 107	164		18%	2.3
Ex. 108	165		0.04	0.09
Ex. 109	166		0.05	0.42
Ex. 110	167		0.3	0.4
Ex. 111	170			0.01
Ex.112	175		2.5	0.5
Ex. 115	187			0.04
Ex. 116	188			0.02

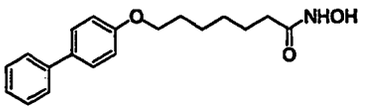
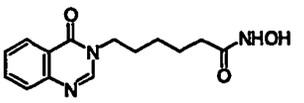
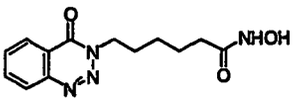
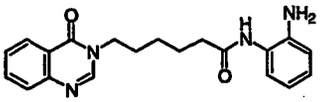
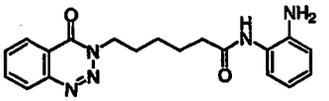
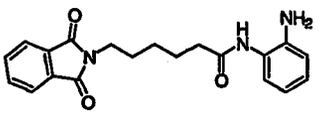
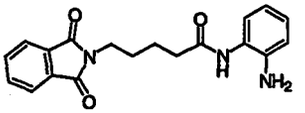
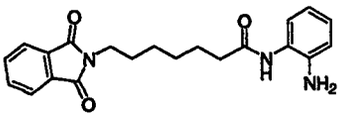
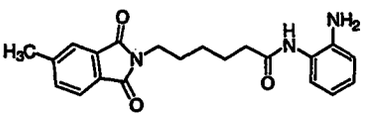
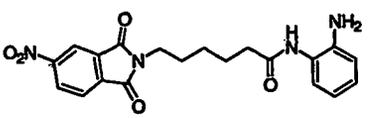
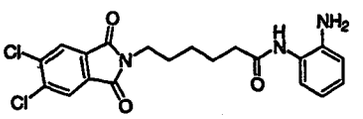
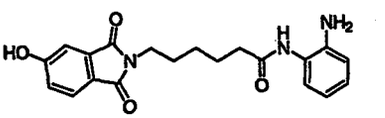
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Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 117	194			24
Ex. 118	198			16
Ex. 119	199		0.08	0.03
Ex. 120	204			5
Ex. 121	205			0.04
Ex. 122	209			0.05
Ex. 123	210			10
Ex. 124	213			3
Ex. 125	216			0.3
Ex. 126	220a			0.02
Ex. 127	220b			0.1
Ex. 128	222			0.1

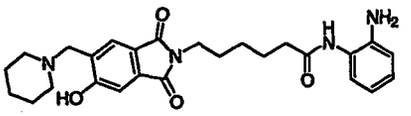
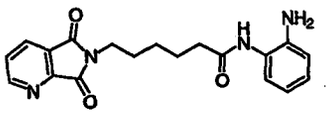
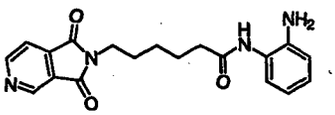
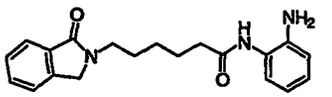
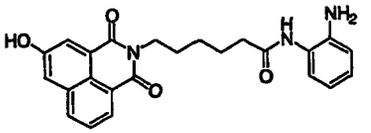
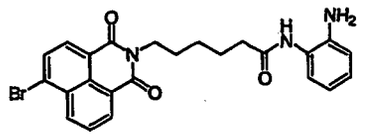
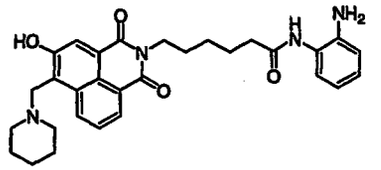
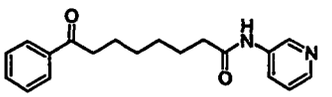
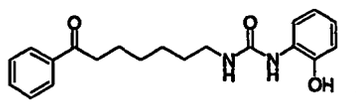
(continued)

Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 129	223			2
Ex. 130	224			3
Ex. 131	226a			0.007
Ex. 132	226b			0.006
Ex. 133	227a			3
Ex. 134	227b			3
Ex. 135	229a			1
Ex. 136	229b			0.04
Ex. 137	230a			5
Ex. 138	230b			12
Ex. 139	234			1

(continued)

Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 140	235			0.004
Ex. 141	238a		0% @1μM	0.05
Ex. 142	238b		20% @1μM	0.76
Ex. 143	239a		0%	11.6
Ex. 144	239b		14%	8.1
Ex. 145	243a		6%	1.6
Ex. 146	243b			99
Ex. 147	243c			4
Ex. 148	243d			3
Ex. 149	243e			12
Ex. 150	243f			3
Ex. 151	243g			3

(continued)

Example	Cpd.	Structure	pooled HDACs IC_{50} (μM)	rHDAC-1 IC_{50} (μM)
Ex. 152	243h			3
Ex. 153	246a			5
Ex. 154	246b			14
Ex. 155	248			4
Ex. 156	251a		0%	0.7
Ex. 157	251b			1
Ex. 158	251c			2
	252		0%	> 20
	253		0%	> 20
" Unless otherwise indicated, inhibition values expressed in percent refer to the percent inhibition at 20 μM.				

Example 160:

Inhibition of Histone Deacetylase in Whole Cells

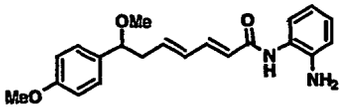
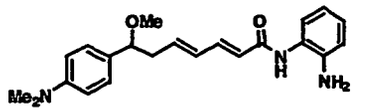
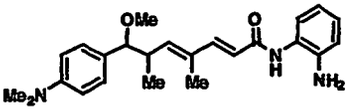
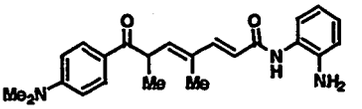
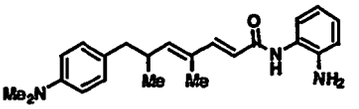
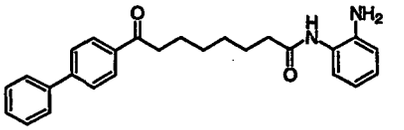
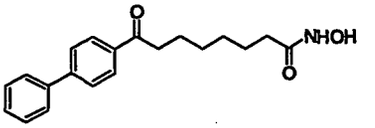
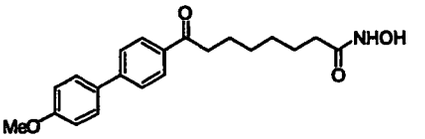
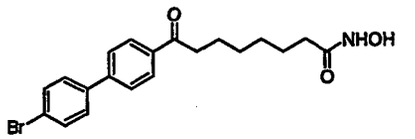
1. Histone H4 acetylation in whole cells by immunoblots

[0499] T24 human bladder cancer cells growing in culture were incubated with HDAC inhibitors for 16 hours. Histones were extracted from the cells after the culture period as described by M. Yoshida et al. (J. Biol. Chem. 265(28):

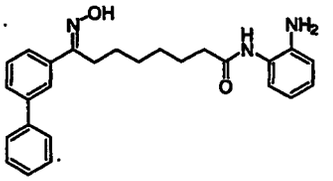
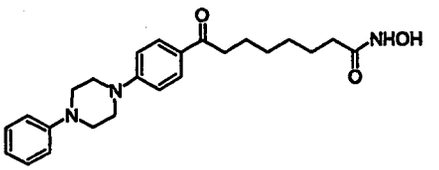
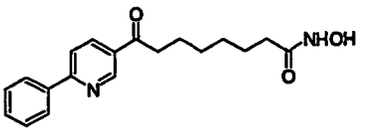
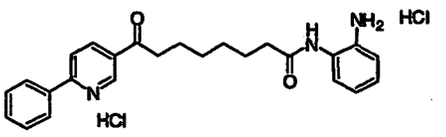
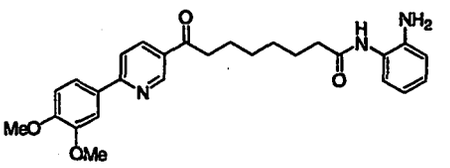
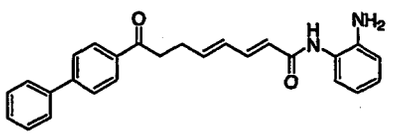
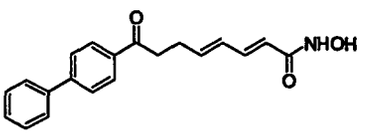
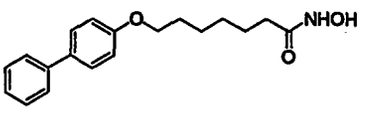
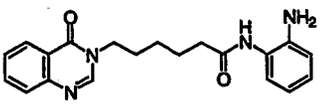
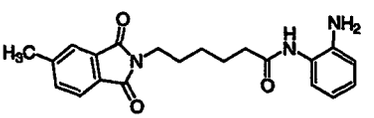
17174-17179 (1990)). 20 μg of total histone protein was loaded onto SDS/PAGE and transferred to nitrocellulose membranes. Membranes were probed with polyclonal antibodies specific for acetylated histone H-4 (Upstate Biotech Inc.), followed by horse radish peroxidase conjugated secondary antibodies (Sigma). Enhanced Chemiluminescence (ECL) (Amersham) detection was performed using Kodak films (Eastman Kodak). Acetylated H-4 signal was quantified by densitometry.

[0500] Data for selected compounds are presented in Table 3. Data are presented as the concentration effective for reducing the acetylated H-4 signal by 50% (EC_{50}).

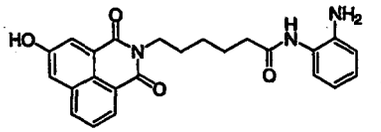
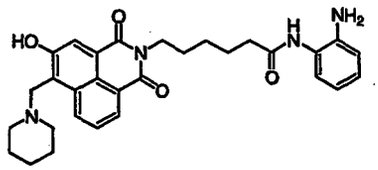
Table 3: Inhibition of Histone Acetylation in Cells

Example	Cpd.	Structure	EC_{50} (μM)
Ex. 4	18		10
Ex. 6	20		5
Ex. 12	34		5
Ex. 13	35		5
Ex. 15	39		10
Ex. 32	77		10
Ex. 33	78		10
Ex. 69	120		10
Ex. 70	124		3

(continued)

Example	Cpd.	Structure	EC_{50} (μM)
Ex. 78	134		10
Ex. 86	138g		5
Ex. 91	145		10
Ex. 92	146		5
Ex. 94	151		3
Ex. 120	204		15
Ex. 121	205		3
Ex. 140	235		5
Ex. 143	239a		5
Ex. 148	243d		3

(continued)

Example	Cpd.	Structure	EC_{50} (μM)
Ex. 156	251a		5
Ex. 158	251c		1

2. Acid Urea Triton (AUT) gel analysis of histone acetylation.

[0501] Human cancer cells (T24, 293T or Jurkat cells) growing in culture are incubated with HDAC inhibitors for 24 h Histones are extracted from the cells as described by M. Yoshida et al. (J. Biol. Chem. 265(28): 17174-17179 (1990)). Acid urea triton (AUT) gel electrophoresis is used for detection of acetylated histone m olecules. Histones (150 μg of total protein) are electrophoresed at 80 V for 16 h at room temperature as described by M. Yoshida *et al., supra.* Gels are stained with Coomassie brilliant blue to visualize histones, dried and scanned by densitometry to quantified acetylation of histones.

Example 161:

Antineoplastic Effect of Histone Deacetylase Inhibitors on Tumor Cells *In Vivo*

[0502] Eight to ten week old female BALB/c nude mice (Taconic Labs, Great Barrington, NY) were injected subcutaneously in the flank area with 2 x 10^6 preconditioned A549 human lung carcinoma cells. Preconditioning of these cells was accomplished by a minimum of three consecutive tumor transplantations in the same strain of nude mice. Subsequently, tumor fragments of approximately 30 mgs were excised and implanted subcutaneously in mice, in the left flank area, under isoflurane anesthesia (Abbott Labs, Geneva, Switzerland). When the tumors reached a mean volume of 100 mm^3, the mice were treated intravenously, subcutaneously or intraperitoneally, by daily injection of a solution of the inhibitor in an appropriate vehicle such as PBS, DMSO/water, or Tween 80/water, at a dose from about 10 mg/kg to about 50 mg/kg, for 21 days. Tumor volume was calculated every second day post infusion according to standard methods (*e.g.*, Meyer et al., Int. J. Cancer 43: 851-856 (1989)). Treatment with compound **34** caused a significant reduction in tumor weight and volume relative to controls treated with saline only (*i.e.*, no HDAC inhibitor). In addition, the activity of histone deacetylase, when measured, is expected to be significantly reduced relative to saline treated controls.

Example 162:

Synergistic Antineoplastic Effect of Histone Deacetylase Inhibitors and Histone Deacetylase Antisense Oligonucleotides on Tumor Cells In Vivo

[0503] The purpose of this example is to illustrate the ability of the histone deacetylase inhibitor of the invention and a histone deacetylase antisense oligonucleotide to synergistically inhibit tumor growth in a mammal. Preferably, the antisense oligonucleotide and the HDAC inhibitor inhibit the expression and activity of the same histone deacetylase.

[0504] As described in Example 161, mice bearing implanted A549 tumors (mean volume 100 mm^3) are treated daily with saline preparations containing from about 0.1 mg to about 30 mg per kg body weight of histone deacetylase antisense oligonucleotide. A second group of mice is treated daily with pharmaceutically acceptable preparations containing from about 0.01 mg to about 5 mg per kg body weight of HDAC inhibitor.

[0505] Some mice receive both the antisense oligonucleotide and the HDAC inhibitor. Of these mice, one group may receive the antisense oligonucleotide and the HDAC inhibitor simultaneously intravenously via the tail vein. Another group may receive the antisense oligonucleotide via the tail vein, and the HDAC inhibitor subcutaneously. Yet another group may receive both the antisense oligonucleotide and the HDAC inhibitor subcutaneously. Control groups of mice

are similarly established which receive no treatment (*e.g.*, saline only), a mismatch antisense oligonucleotide only, a control compound that does not inhibit histone deacetylase activity, and a mismatch antisense oligonucleotide with a control compound.

[0506] Tumor volume is measured with calipers. Treatment with the antisense oligonucleotide plus the histone deacetylase protein inhibitor according to the invention causes a significant reduction in tumor weight and volume relative to controls.

Claims

1. An inhibitor of histone deacetylase represented by formula (1):

$$Cy\text{-}X\text{-}Y^1\text{-}W \qquad (1)$$

wherein
Cy is cycloalkyl, aryl, or a radical of a heterocyclic moiety, any of which may be optionally substituted;
X is selected from the group consisting of C=O, $C{=}CH_2$, CH(OH), $CH(OR^1)$, C=N(OH), and $C{=}N(OR^1)$, where R^1 is alkyl, aryl, aralkyl, or acyl and where alkyl is a straight or branched chain saturated aliphatic group having from 1 to 12 carbon atoms, which may be substituted with one, two or three substituents;
Y^1 is a saturated C_3-C_7 alkylene, wherein said alkylene may be optionally substituted, and wherein one or two carbon atoms in the linear chain connecting X and W may be replaced with O, NR^3, or $S(O)_n$, where R^3 is hydrogen, alkyl, aryl, aralkyl, sulfonyl, acyl, alkoxycarbonyl, or carbamoyl, and n is 0, 1, or 2, provided that the atoms in Y^1 that are attached to X and W are carbon atoms, and further provided that Y^1 does not comprise an ester or amide linkage in the linear chain connecting X and W; and
W is selected from the group consisting of $-C(O)-CH_2-SR^2$, -C(O)-NH-OM,-NH-C(O)-NH-Z, and -C(O)-NH-Z, where R^2 is alkyl, aryl, aralkyl, or acyl, wherein the aryl portion of any such groups may be optionally substituted;
M is hydrogen or a pharmaceutically acceptable cation;
Z is selected from the group consisting of anilinyl, pyridyl, thiazolyl, hydroxyphenyl, thiadiazolyl, anilinylmethyl, or pyridylinethyl, any of which groups optionally may be substituted with halo, hydroxyl, amino, nitro, C_1-C_4 alkyl, or C_1-C_4 alkoxy;
provided that X is $C{=}CH_2$, $CH(OR^1)$, C=N(OH), or $C{=}N(OR^1)$ when W is -C(O)-NH-OM and Cy is unsubstituted phenyl, dimethylaminophenyl, or methoxyphenyl; and
further provided that when W is $-C(O)-CH_2-SR^2$, the carbon atom in Y^1 that is attached to W is unsubstituted or is substituted with other than amino, acylamino, alkoxycarbonyl, or carbamoyl; and
further provided that when Cy is 2-methoxy-naphtyl, X is C=O and bounded to the position 6 of the said naphtyl, Y^1 is $(CH_2)_4$, W is different from C=O-NHOH, C=O-2-thiazolylamino, C=O-4-hydroxyanilino or C=O-2-hydroxyanilino.

2. The inhibitor of claim 1, wherein Cy is C_6- C_{10} aryl or is a radical of a heterocyclic moiety selected from the group consisting of thiophene, benzothiophene, furan, benzofuran, pyridine, quinoline, indole, isoquinoline, thiazole, morpholine, piperidine, and piperazine, any of which groups may be optionally substituted.

3. The inhibitor of claim 2, wherein the aryl or heterocyclic moiety is substituted by one or two substituents independently selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_6-C_{10} aryl, heteroaryl, heterocyclyl, (C_6-C_{10})ar(C_1-C_6)alkyl, halo, nitro, hydroxyl, C_1-C_6 alkoxy, C_6-C_{10} aryloxy, heteroaryloxy, C_1-C_6 alkoxycarbonyl, C_6-C_{410} aryloxycarbonyl, heteroaryloxycarbonyl, carboxy, and amino.

4. The inhibitor of claim 1, wherein Cy has the formula $-Cy^1-Cy^2$ or Cy^1-G-Cy^2, wherein Cy^1 and Cy^2 are independently C_3-C_6 cycloalkyl, C_6-C_{10} aryl, or a radical of a heterocyclic moiety, which groups optionally may be substituted, and G or O, NR3 or $S(O)_n$ where R^3 is hydrogen alkyl, aryl, aralkyl, sulfonyl, acyl, alkoxycarbonyl, or carbamoyl, and n is 0, 1, or 2.

5. The inhibitor of claim 4, wherein Cy^1 and Cy^2 are independently selected from the group consisting of phenyl, pyridinyl, morpholinyl, piperidinyl, piperazinyl, which groups optionally may be substituted.

6. The inhibitor of claim 1, where X is selected from the group consisting of $CH(OR^1)$, C=N(OH), and $C{=}N(OR^1)$, where R^1 is C_1-C_6 alkyl, C_6-C_{10} aryl, or (C_6-C_{10})ar(C_1-C_6)alkyl.

7. The inhibitor of claim 1, wherein one to about three carbon atoms of the alkylene are independently substituted with

halo, oxo, oximino, nitro, haloalkyl, alkyl, aralkyl, alkoxy, aryloxy, alkoxycarbonyl, carboxy, hydroxyalkyl, acyl, acyloxy, or cyano.

8. The inhibitor of claim 1, wherein Y^1 comprises an all carbon linear chain connecting X and W.

9. The inhibitor of claim 8, wherein Y^1 is $-(CH_2)_m$, where m is 5, 6, or 7.

10. The inhibitor of claim 1, wherein one carbon atom in the linear chain connecting X and W is replaced with O, NR^3, or $S(O)_n$.

11. The inhibitor of claim 10, wherein Y^1 is $-(CH_2)-S(O)_n-(CH_2)_p$, where n is 0, 1, or 2, and p is 3, 4, or 5.

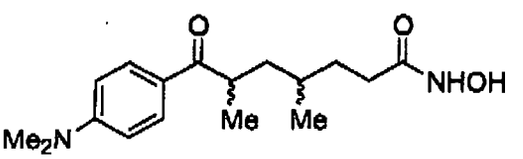
12. The inhibitor of claim 1, wherein W is -C(O)-NH-OM, M being selected from the group consisting of hydrogen, sodium, potassium, magnesium, and calcium.

13. The inhibitor of claim 1, wherein W is -C(O)-NH-Z or -NH-Z, Z being unsubstituted 2-anilinyl or unsubstituted 2-pyridyl.

14. The inhibitor of claim 1, wherein W is $-C(O)-CH_2-SR^2$, R^2 being selected from the group consisting of C_1-C_6 alkyl, C_6-C_{10} aryl, (C_6-C_{10})ar(C_1-C_6)alkyl, (C_1-C_6 alkyl)carbonyl, (C_6-C_{10} aryl)carbonyl, and ((C_6-C_{10})ar(C_1-C_6)alkyl)carbonyl, wherein the aryl portion of any such groups may be optionally substituted.

15. The inhibitor of claim 14, wherein R^2 is selected from the group consisting of methyl, phenyl, benzyl, benzoyl, and acetyl.

16. An inhibitor of histone deacetylase represented by formulae (5):



(5)

17. A pharmaceutical composition comprising the inhibitor of histone deacetylase of claim 1 and a pharmaceutically acceptable carrier, excipient, or diluent.

18. A pharmaceutical composition comprising the inhibitor of histone deacetylase of claim 16 and a pharmaceutically acceptable carrier, excipient, or diluent.

19. Use of an inhibitor of histone deacetylase of claim 1 for the manufacture of a medicament for the treatment of a cell proliferative disease, of a protozoal disease or of a fungal disease.

20. Use of an inhibitor of histone deacetylase of claim 16 for the manufacture of a medicament for the treatment of a cell proliferative disease, of a protozoal disease or of a fungal disease.

Patentansprüche

1. Histon-Deacetylase-Inhibitor, dargestellt durch die Formel (1):

$$Cy\text{-}X\text{-}Y^1\text{-}W \qquad (1)$$

wobei
Cy für Cycloalkyl, Aryl oder ein Radikal einer heterocyclischen Gruppe steht, die gegebenenfalls jeweils substituiert sein können;
X aus der Gruppe bestehend aus C=O, $C=CH_2$, CH(OH), $CH(OR^1)$, C=N(OH) und $C=N(OR^1)$ ausgewählt ist, wobei R^1 für Alkyl, Aryl, Aralkyl oder Acyl steht, und wobei Alkyl eine gerad- oder verzweigtkettige gesättigte aliphatische

Gruppe mit 1 bis 12 Kohlenstoffatomen ist, die mit einem, zwei oder drei Substituenten substituiert sein kann;
Y^1 für ein gesättigtes C_3-C_7-Alkylen steht, wobei das Alkylen gegebenenfalls substituiert sein kann, und wobei ein oder zwei Kohlenstoffatome in der linearen Kette, die X und W verbindet, durch O, NR^3 oder $S(O)_n$ ersetzt sein kann, wobei R^3 für Wasserstoff, Alkyl, Aryl, Aralkyl, Sulfonyl, Acyl, Alkoxycarbonyl oder Carbamoyl steht, und n für 0, 1 oder 2 steht, vorausgesetzt, dass die Atome in Y^1, die an X und W gebunden sind, Kohlenstoffatome sind, und ferner vorausgesetzt, dass Y^1 keine Ester- oder Amidbindung in der linearen Kette aufweist, die X und W verbindet; und
W aus der Gruppe bestehend aus -C(O)-CH_2-SR^2, -C(O)-NH-OM,- NH-C(O)-NH-Z und -C(O)-NH-Z ausgewählt ist, wobei
R^2 für Alkyl, Aryl, Aralkyl oder Acyl steht, wobei der Arylteil aller solcher Gruppen gegebenenfalls substituiert sein kann;
M für Wasserstoff oder ein pharmazeutisch unbedenkliches Kation steht;
Z aus der Gruppe bestehend as Anilinyl, Pyridyl, Thiazolyl, Hydroxyphenyl, Thiadiazolyl, Anilinylmethyl oder Pyridylmethyl ausgewählt ist, wobei jede von diesen Gruppen gegebenenfalls durch Halo, Hydroxyl, Amino, Nitro, C_1-C_4-Alkyl oder C_1-C_4-Alkoxy substituiert sein kann;
vorausgesetzt, dass X für $C=CH_2$, $CH(OR^1)$, C=N(OH) oder $C=N(OR^1)$ steht, wenn W für -C(O)-NH-OM steht und Cy für unsubstituiertes Phenyl, Dimethylaminophenyl oder Methoxyphenyl steht; und
ferner vorausgesetzt, dass, wenn W für -C(O)-CH_2-SR^2 steht, das Kohlenstoffatom in Y^1, das an W gebunden ist, unsubstituiert ist oder durch andere als Amino, Acylamino, Alkoxycarbonyl oder Carbamoyl substituiert ist; und
ferner vorausgesetzt, dass, wenn Cy für 2-Methoxy-naphtyl steht, X für C=O steht und an die Position 6 des Naphtyls gebunden ist, Y^1 für $(CH_2)_4$ steht, W verschieden von C=O-NHOH, C=O-2-Thiazolylamin, C=O-4-Hydroxyanilin oder C=O-2-Hydroxyanilin ist.

2. Inhibitor nach Anspruch 1, wobei Cy für C_6-C_{10}-Aryl steht oder für ein Radikal einer heterocyclischen Gruppe steht, die aus der Gruppe bestehend aus Thiophen, Benzothiophen, Furan, Benzofuran, Pyridin, Chinolin, Indol, Isochinolin, Thiazol, Morpholin, Piperidin und Piperazin ausgewählt ist, wobei jede von diesen Gruppen gegebenenfalls substituiert sein kann.

3. Inhibitor nach Anspruch 2, wobei die Aryl- oder heterocycische Gruppe durch einen oder zwei Substituenten substituiert ist, die unabhängig voneinander aus der Gruppe bestehend aus C_1-C_4-Alkyl, C_1-C_4-Haloalkyl, C_6-C_{10}-Aryl, Heteroaryl, Heterocyclyl, (C_6-C_{10})-Ar-(C_1-C_6)-Alkyl, Halo, Nitro, Hydroxyl, C_1-C_6-Alkoxy, C_6-C_{10}-Aryloxy, Heteroaryloxy, C_1-C_6-Alkoxycarbonyl, C_6-C_{10}-Aryloxycarbonyl, Heteroaryloxycarbonyl, Carboxy und Amino ausgewählt sind.

4. Inhibitor nach Anspruch 1, wobei Cy die Formel -Cy^1-Cy^2 oder Cy^1-G-Cy^2 aufweist, wobei Cy^1 und Cy^2 unabhängig voneinander für C_3-C_6-Cycloalkyl, C_6-C_{10}-Aryl oder ein Radikal einer heterocyclischen Gruppe stehen, wobei die Gruppen gegebenenfalls substituiert sein können, und G oder O, NR^3 oder $S(O)_n$, wobei R^3 für Wasserstoff, Alkyl, Aryl, Aralkyl, Sulfonyl, Acyl, Alkoxycarbonyl oder Carbamoyl steht, und n für 0, 1 oder 2 steht.

5. Inhibitor nach 4, wobei Cy^1 und Cy^2 unabhängig voneinander aus der Gruppe bestehend aus Phenyl, Pyridinyl, Morpholinyl, Piperidinyl, Piperazinyl ausgewählt sind, wobei die Gruppen gegebenenfalls substituiert sein können.

6. Inhibitor nach Anspruch 1, wobei X aus der Gruppe bestehend aus $CH(OR^1)$, C=N(OH) und $C=N(OR^1)$ ausgewählt ist, wobei R^1 für C_1-C_6-Alkyl, C_6-C_{10}-Aryl oder (C_6-C_{10})-Ar-(C_1-C_6)-Alkyl steht.

7. Inhibitor nach Anspruch 1, wobei ein bis etwa drei Kohlenstoffatome des Alkylens unabhängig voneinander durch Halo, Oxo, Oximino, Nitro, Haloalkyl, Alkyl, Aralkyl, Alkoxy, Aryloxy, Alkoxycarbonyl, Carboxy, Hydroxyalkyl, Acyl, Acyloxy oder Cyano substituiert sind.

8. Inhibitor nach Anspruch 1, wobei Y^1 eine lineare Ganzkohlenstoffkette umfasst, die X und W verbindet.

9. Inhibitor nach Anspruch 8, wobei Y^1 für -$(CH_2)_m$ steht, und wobei m für 5, 6 oder 7 steht.

10. Inhibitor nach Anspruch 1, wobei ein Kohlenstoffatom oder linearen Kette, die X und W verbindet, durch O, NR^3, oder $S(O)_n$ ersetzt ist.

11. Inhibitor nach Anspruch 10, wobei Y^1 für -(CH_2)-$S(O)_n$-$(CH_2)_p$ steht, wobei n für 0, 1 oder 2 steht und p für 3, 4 oder 5 steht.

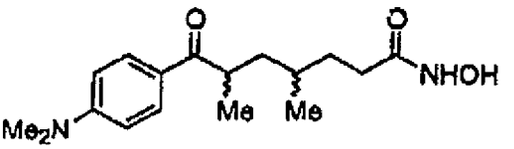
12. Inhibitor nach Anspruch 1, wobei W für -C(O)-NH-OM steht, wobei M aus der Gruppe bestehend aus Wasserstoff, Natrium, Kalium, Magnesium und Calcium ausgewählt ist.

13. Inhibitor nach Anspruch 1, wobei W für -C(O)-NH-Z oder -NH-Z steht, wobei Z unsubstituiertes 2-Anilinyl oder unsubstituiertes 2-Pyridyl ist.

14. Inhibitor nach Anspruch 1, wobei W für -C(O)-CH_2-SR^2 steht, wobei R^2 aus der Gruppe bestehend aus C_1-C_6-Alkyl, C_6-C_{10}-Aryl, (C_6-G_{10})-Ar-(C_1-C_6)-Alkyl, (C_1-C_6-Alkyl)carbonyl, (C_6-C_{10}-Aryl)carbonyl und ((C_6-C_{10})-Ar-(C_1-C_6)-Alkyl)carbonyl ausgewählt ist, wobei der Arylteil aller solcher Gruppen gegebenenfalls substituiert sein kann.

15. Inhibitor nach Anspruch 14, wobei R^2 aus der Gruppe bestehend aus Methyl, Phenyl, Benzoyl, Benzoyl und Acetyl ausgewählt ist.

16. Histon-Deacetylase-Inhibitor, dargestellt durch die Formel (5):



(5)

17. Pharmazeutische Zusammensetzung, die den Histon-Deacetylase-Inhibitor nach Anspruch 1 und einen pharmazeutisch unbedenklichen Träger, Hilfsstoff oder Verdünner umfasst.

18. Pharmazeutische Zusammensetzung, die den Histon-Deacetylase-Inhibitor nach Anspruch 16 und einen pharmazeutisch unbedenklichen Träger, Hilfsstoff oder Verdünner umfasst.

19. Verwendung eines Histon-Deacetylase-Inhibitors nach Anspruch 1 zur Herstellung eines Medikaments für die Behandlung einer zellproliferativen Erkrankung, einer durch Protozoen verursachten Erkrankung oder einer Pilzerkrankung.

20. Verwendung eines Histon-Deacetylase-Inhibitors nach Anspruch 16 zur Herstellung eines Medikaments für die Behandlung einer zellproliferativen Erkrankung, einer durch Protozoen verursachten Erkrankung oder einer Pilzerkrankung.

Revendications

1. Inhibiteur d'histone désacétylase représentée par la formule (1) :

Cy-X-Y^1-W (1)

dans laquelle
Cy est un groupe cycloalkyle, aryle, ou un radical de fragment hétérocyclique, dont l'un quelconque peut être facultativement substitué ;
X est choisi dans le groupe consistant en C=O, $C=CH_2$, CH(OH), $CH(OR^1)$, C=N(OH) et $C=N(OR^1)$, où R^1 est un groupe alkyle, aryle, aralkyle ou acyle et où le groupe alkyle est un groupe aliphatique saturé à chaîne droite ou ramifiée comportant 1 à 12 atomes de carbone, qui peut être substitué par un, deux ou trois substituants ;
Y^1 est un groupe alkylène en C_3 à C_7 saturé, où ledit groupe alkylène peut être facultativement substitué et où un ou deux atomes de carbone dans la chaîne linéaire reliant X et W peuvent être remplacés par O, NR^3 ou $S(O)_n$, où R^3 est un atome d'hydrogène, un groupe alkyle, aryle, aralkyle, sulfonyle, acyle, alcoxycarbonyle ou carbamoyle, et n vaut 0, 1 ou 2, à condition que les atomes dans Y^1 qui sont attachés à X et W soient des atomes de carbone, et en outre à condition que Y^1 ne comprenne pas une liaison ester ou amide dans la chaîne linéaire reliant X et W ; et
W est choisi dans le groupe consistant en -C(O)-CH_2-SR^2, -C(O)-NH-OM, -NH-C(O)-NH-Z et -C(O)-NH-Z, où
R^2 est un groupe alkyle, aryle, aralkyle ou acyle, où la portion aryle de l'un quelconque de ces groupes peut être facultativement substituée ;

M est un atome d'hydrogène ou un cation pharmaceutiquement acceptable ;
Z est choisi dans le groupe consistant en un groupe anilinyle, pyridyle, thiazolyle, hydroxyphényle, thiadiazolyle, anilinylméthyle ou pyridylméthyle, l'un quelconque de ces groupes pouvant facultativement être substitué par un groupe halogéno, hydroxyle, amino, nitro, alkyle en C_1 à C_4 ou alcoxy en C_1 à C_4 ;
à condition que X soit $C=CH_2$, $CH(OR^1)$, $C=N(OH)$ ou $C=N(OR^1)$ lorsque W est -C(O)-NH-OM et Cy est un groupe phényle, diméthylaminophényle ou méthoxyphényle non substitué ; et
en outre à condition que lorsque W est $-C(O)-CH_2-SR^2$, l'atome de carbone dans Y^1 qui est attaché à W soit non substitué ou soit substitué par un groupe autre qu'un groupe amino, acylamino, alcoxycarbonyle ou carbamoyle ; et
en outre à condition que lorsque Cy est un groupe 2-méthoxy-naphtyle, X soit C=O et soit lié à la position 6 dudit groupe naphtyle, Y^1 soit $(CH_2)_4$, W soit différent de C=O-NHOH, un groupe C=O-2-thiazolylamino, C=O-4-hydroxyanilino ou C=O-2-hydroxyanilino.

2. Inhibiteur selon la revendication 1, dans lequel Cy est un groupe aryle en C_6 à C_{10} ou est un radical d'un fragment hétérocyclique choisi dans le groupe consistant en thiophène, benzothiophène, furane, benzofurane, pyridine, quinoléine, indole, isoquinoléine, thiazole, morpholine, pipéridine et pipérazine, l'un quelconque de ces groupes pouvant être facultativement substitué.

3. Inhibiteur selon la revendication 2, dans lequel le fragment aryle ou hétérocyclique est substitué par un ou deux substituants choisis indépendamment dans le groupe constitué par un groupe alkyle en C_1 à C_4, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, hétéroaryle, hétérocyclyle, aryl(en C_6 à C_{10})alkyle(en C_1 à C_6), halogéno, nitro, hydroxyle, alcoxy en C_1 à C_6, aryloxy en C_6 à C_{10}, hétéroaryloxy, alcoxycarbonyle en C_1 à C_6, aryloxycarbonyle en C_6 à C_{10}, hétéroaryloxycarbonyle, carboxy et amino.

4. Inhibiteur selon la revendication 1, dans lequel Cy a la formule $-Cy^1-Cy^2$ ou Cy^1-G-Cy^2, où Cy^1 et Cy^2 sont indépendamment un groupe cycloalkyle en C_3 à C_6, aryle en C_6 à C_{10}, ou un radical d'un fragment hétérocyclique, lesquels groupes peuvent facultativement être substitués, et G ou O, NR^3 ou $S(O)_n$ où R^3 est un atome d'hydrogène, un groupe alkyle, aryle, aralkyle, sulfonyle, acyle, alcoxycarbonyle ou carbamoyle, et n vaut 0, 1 ou 2.

5. Inhibiteur selon la revendication 4, dans lequel Cy^1 et Cy^2 sont indépendamment choisis dans le groupe consistant en un groupe phényle, pyridinyle, morpholinyle, pipéridinyle, pipérazinyle, lesquels groupes peuvent facultativement être substitués.

6. Inhibiteur selon la revendication 1, où X est choisi dans le groupe consistant en $CH(OR^1)$, $C=N(OH)$ et $C=N(OR^1)$, où R^1 est un groupe alkyle en C_1 à C_6, aryle C_6 à C_{10} ou aryl(en C_6 à C_{10})alkyle(en C_1 à C_6).

7. Inhibiteur selon la revendication 1, dans lequel un à environ trois atomes de carbone du groupe alkylène sont indépendamment substitués par un groupe halogéno, oxo, oximino, nitro, halogénoalkyle, alkyle, aralkyle, alcoxy, aryloxy, alcoxycarbonyle, carboxy, hydroxyalkyle, acyle, acyloxy ou cyano.

8. Inhibiteur selon la revendication 1, dans lequel Y^1 comprend une chaîne linéaire exclusivement de carbone reliant X et W.

9. Inhibiteur selon la revendication 8, dans lequel Y^1 est $-(CH_2)_m$, où m vaut 5, 6 ou 7.

10. Inhibiteur selon la revendication 1, dans lequel un atome de carbone dans la chaîne linéaire reliant X et W est remplacé par O, NR^3 ou $S(O)_n$.

11. Inhibiteur selon la revendication 10, où Y^1 est $-(CH_2)-S(O)_n-(CH_2)_p$, où n vaut 0, 1 ou 2, et p vaut 3, 4 ou 5.

12. Inhibiteur selon la revendication 1, dans lequel W est -C(O)-NH-OM, M étant choisi dans le groupe consistant en l'hydrogène, le sodium, le potassium, le magnésium et le calcium.

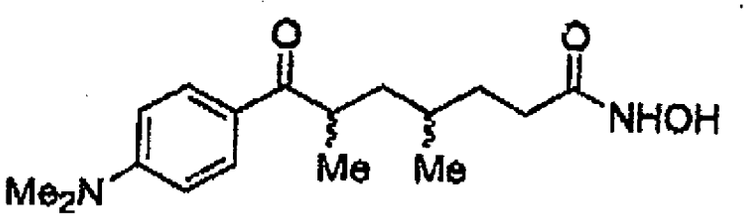
13. Inhibiteur selon la revendication 1, dans lequel W est -C(O)-NH-Z ou NH-Z, Z étant un groupe 2-anilinyle non substitué ou 2-pyridyle non substitué.

14. Inhibiteur selon la revendication 1, dans lequel W est $-C(O)-CH_2-SR^2$, R^2 étant choisi dans le groupe consistant en un groupe alkyle en C_1 à C_6, aryle en C_6 à C_{10}, aryl(en C_6 à $_{10}$)alkyle(en C_1 à C_6), (alkyl en C_1 à C_6)carbanyle,

(aryl en C_6 à C_{10})carbonyle et (aryl(en C_6 à C_{10})alkyl(en C_1 à C_6))carbonyle, où la portion aryle de l'un quelconque de ces groupes peut être facultativement substituée.

15. Inhibiteur selon la revendication 14, où R^2 est choisi dans le groupe consistant en les groupes méthyle, phényle, benzyle, benzoyle et acétyle.

16. Inhibiteur d'histone désacétylase représentée par la formule (5) :



(5)

17. Une composition pharmaceutique comprenant l'inhibiteur d'histone désacétylase selon la revendication 1 et un support, un excipient ou un diluant pharmaceutiquement acceptable.

18. Une composition pharmaceutique comprenant l'inhibiteur d'histone désacétylase selon la revendication 16 et un support, un excipient ou un diluant pharmaceutiquement acceptable.

19. Utilisation d'un inhibiteur d'histone désacétylase selon la revendication 1 pour la fabrication d'un médicament pour le traitement de maladies à prolifération de cellules, de maladies à protozoaires ou de mycoses.

20. Utilisation d'un inhibiteur d'histone désacétylase selon la revendication 16 pour la fabrication d'un médicament pour le traitement de maladies à prolifération de cellules, de maladies à protozoaires ou de mycoses.

REFERENCES CITED IN THE DESCRIPTION

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